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The efficacy of ascorbic acid in the prevention of complex regional pain syndrome (type 1) following distal radial fracture

THE EFFICACY OF ASCORBIC ACID IN THE PREVENTION OF COMPLEX REGIONAL PAIN SYNDROME (TYPE 1) FOLLOWING DISTAL RADIAL FRACTURE

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ABSTRACT

Complex regional pain syndrome (CRPS) is a common problem presenting to orthopaedic surgeons or pain therapists, most frequently encountered following trauma. The cardinal features are of pain, hypersensitivity, vasomotor instability and joint stiffness. The exact cause remains unproven, however an exaggerated inflammatory response and free radical induced cellular damage has been proposed. A small number of previous studies have highlighted a potential role for antioxidants in the prevention of the condition.

Over the last three decades pain researchers have developed and agreed on a set of modified International Association of the Study of Pain (IASP) diagnostic criteria. Orthopaedic researchers have developed their own criteria that have been subject to much debate as to their validity.

The diagnosis of CRPS in two hundred and sixty-two patients from a previous study have been reanalysed using the Atkins and modified IASP diagnostic criteria of Bruehl. The incidence of CRPS was similar using either criteria (Bruehl 20.61% vs. Atkins 22.52%). Using the Bruehl criteria as a gold standard, there was strong diagnostic agreement ($\kappa = 0.79$, sensitivity = 0.87, specificity = 0.94).

Two hundred and eleven patients who had sustained an isolated distal radial fracture were recruited for a prospective double-blinded randomised control trial to assess the efficacy of five hundred milligrams of ascorbic acid in order to prevent CRPS.

Using an intention to treat analysis one hundred and ninety-six were reviewed at a minimum of nine weeks. There was no significant difference in the incidence of CRPS (chi-squared=1.196, p=0.305) or the incidence or severity of the individual features of the condition between the two treatment groups.

The results of this study suggest that prophylaxis with ascorbic acid does not prevent the occurrence of CRPS when diagnosed with validated criteria following a distal radial fracture.

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AUTHOR'S DECLARATION

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award.

Except where indicated by specific reference in the text, the work is the candidate's own work. Any views expressed in the dissertation are those of the author.

The pharmacy production unit at the Bristol Royal Infirmary prepared all medications.

The dolorimeter was made by the Medical Equipment Management Organisation at the Bristol Royal Infirmary.

This study and thesis was completed and written by myself under the guidance of my supervisor, Professor Roger Atkins MA DM FRCS, Consultant Orthopaedic Surgeon, Bristol Royal Infirmary and visiting Professor of Trauma & Orthopaedic Surgery, University of Bristol.

SIGNED: ..... DATE:.....

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LIST OF ABBREVIATIONS

CRPS	complex regional pain syndrome
IASP	International Association for the Study of Pain
RSD	reflex sympathetic dystrophy
MRI	magnetic resonance imaging
VMI	vasomotor instability
CGRP	calcitonin gene related peptide
ACE	angiotensin-converting enzyme
HLA	human leukocyte antigen
SNS	sympathetic nervous system
SMP	sympathetically maintained pain
NGF	nerve growth factor
In-111-IgG	indium-111 labelled human non-specific polyclonal immunoglobulin G
CPIP	chronic post-ischaemia pain
VIP	vasoactive intestinal peptide
NK-1	neurokinin-1
NF-κB	nuclear factor kappa B
IL-1	interleukin-1
IL-6	interleukin-6
TNF-α	tumour necrosis factor alpha
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid

RDA	recommended daily allowance
TAM	total active motion
TPM	total passive motion
AROM	active range of motion
COSMIN	Consensus-based Standards for the selection of health Measurement Instruments
CI	confidence interval
VAS	Visual Analogue Scale
NRS	Numeric Rating Scale
VDS	Verbal Descriptor Scale

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CHAPTER ONE

INTRODUCTION

1 INTRODUCTION

1.1 BACKGROUND

Complex regional pain syndrome (CRPS) is a disabling chronic pain condition of unknown aetiology. It has been the subject of much debate and research since its first classical description in the 19th century. Despite advances over the last few decades in our understanding of this condition, many elements remain unanswered. This study's broad aims are to further extend these advances both in the conundrum of diagnosis and possible prevention of the condition in the trauma setting.

CRPS is most commonly encountered following trauma to a limb and is diagnosed clinically by the presence of abnormal pain, sensory changes, swelling, vasomotor instability, joint stiffness, motor dysfunction, trophic changes and increased sudomotor activity. These symptoms and signs are characteristically out of proportion to the precipitant cause. The nature of these features inevitably has caused the majority of the barriers to the rapid resolution of this condition's exact cause and cure by virtue of the fact that until recently its diagnosis has been varied and the guidance for identifying it disjointed and haphazard amongst the various medical specialists who encounter it.

1.2 TERMINOLOGY

The origins of CRPS can be traced to the 19th Century. Silas Weir Mitchell is credited with the first detailed report in 1864 on an intensely painful condition he termed with colleagues, causalgia (Mitchell et al. 1864). The American Civil War, and the widespread use of low velocity high mass projectiles led Mitchell to treat and observe seven soldiers who had sustained nerve injuries following gunshot wounds. He and his colleagues observed intense burning pain recognising that the worst cases caused "almost unendurable anguish". Also discussed were the now classic skin changes and an early theory on the condition being in part due to a reflex phenomena within the nervous system it self. Without wish to detract from Mitchell's ingenuity it is possible that one of his teachers during his first few years after graduation may have been the first to recognise a syndrome of pain and irregularities of the sympathetic nervous system. The English literature is however sparse on the exact details of Claude Bernard's work from 19th Century Paris.

European researchers dominated the new discoveries being made in pain research at the beginning of the 20th century. In 1900 Südeck made two important contributions. Firstly, only five years after x-rays had been discovered, he described a post-traumatic pain syndrome with oedema, trophic changes and osteoporosis or "Knochenatrophie". Secondly, he postulated an inflammatory ("entzündliche") cause for this observation. Nonne coined the term Südeck's atrophy in 1901. This concept has turned full circle over the last one hundred years and an exaggerated inflammatory response remains firmly in the group of mostly plausible explanations for the mechanism behind CRPS today.

In 1916, Leriche, a French vascular surgeon reported the first successful relief from

the pain associated with causalgia by performing a peri-arterial sympathectomy, thus confirming the work of others before him that the sympathetic nervous plays an important role in the aetiology of the condition.

By the 1930's De Takats had described the concept of a reflex dystrophy of the extremities (De Takats 1937) and based on this and Leriches' work Evans introduced the popular term Reflex Sympathetic Dystrophy in 1947 (Evans 1947). Since then the condition has been described under a number of different guises each one having been popularised depending on the precipitating factor, the country concerned or by the speciality treating the patient (table 1). To avoid a term suggesting aetiology or site the International Association for the Study of Pain (IASP), in 1993, agreed on the new nomenclature of CRPS. Two types of CRPS are currently recognized: type 1, where there is no discernable nerve damage present (formerly termed Reflex Sympathetic Dystrophy) and type 2, where there is a discernable nerve injury (formerly termed causalgia) (Stanton-Hicks et al. 1995).

Table 1 Previous Terms for CRPS

CRPS type 1 (no discernable nerve injury)	**CRPS type 2** (discernable nerve injury)
Reflex sympathetic dystrophy (RSD)	Causalgia
Südeck's atrophy	Major causalgia
Algodystrophy	Mitchell's causalgia
Shoulder hand syndrome	
Painful post traumatic osteoporosis	
Minor causalgia	
Algoneurodystrophy	
Post traumatic pain syndrome	
Painful post traumatic dystrophy	
Transient migratory osteoporosis	

1.3 INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

Fortunately the severe and therefore obvious cases of CRPS are rare following trauma. The more common marginal case however does present a diagnostic challenge without a single gold standard test that can be easily utilised by clinicians. A carefully taken history and initial investigations in these marginal cases should be directed to the exclusion of the common mimickers of the condition.

Adjunct investigations may help but in themselves are not diagnostic. CRPS does not cause elevation of routinely available blood and serum markers of systemic inflammation such as white blood cell count, C-reactive protein and interleukin-6. Other "research-type" systemic markers such as interleukin-8, soluble tumour necrosis factor receptor I/II and substance P may be raised in CRPS (Schinkel et al. 2006). All other routine biochemical indices are also unaffected.

Plain radiography demonstrates features of rapid bone loss: visible demineralisation with patchy, subchondral or sub-periosteal osteoporosis, metaphyseal banding and profound bone loss (Kozin et al. 1976b). Bone involvement is universal with increased uptake on 3-phase bone scanning in early CRPS, this was originally thought to be peri-articular, suggesting arthralgia (Mackinnon et al. 1984; Atkins et al. 1993), however CRPS does not cause arthritis and studies have shown generalised hyperfixation (Bickerstaff et al. 1993). Later the bone scan returns to normal. The debate continues on the reliability of bone scanning with varying results on its sensitivity and specificity, particularly in relation to the duration of CRPS symptoms (O'Donoghue et al. 1993; Lee et al. 1995; Wüppenhorst et al. 2010). The specificity of contrast enhanced Magnetic Resonance Imaging (MRI) can be helpful to exclude other pathologies and in CRPS

may demonstrate skin thickening, early bone and soft tissue oedema, joint effusions and late atrophy with fibrosis but it is not a sensitive screening diagnostic tool in the early phase of post traumatic CRPS (Schürmann et al. 2007).

Temperature difference between the limbs is greater in CRPS than other pain syndromes but again this is not useful screening tool in post traumatic CRPS (Schürmann et al. 2007).

1.4 INCIDENCE

CRPS may occur at any age but it is more common in middle-aged adults. It affects both sexes and all races, but is more common in females.

The full-blown, severe form of CRPS is fortunately rare, reflected by the low prevalence following distal radial fracture in historical retrospective studies (Bacorn et al. 1953; Plewes 1956; Green et al. 1956; Frykman 1967; Cooney et al. 1980).

Prospective studies specifically designed to identify the occurrence of CRPS have consistently shown that a mild form of the condition occurs commonly following trauma or surgical insult. Different research groups have reported an incidence of 11-37% following distal radial fractures over the last three decades (Atkins et al. 1989a; Roumen et al. 1991; Bickerstaff et al. 1994; Field et al. 1997; Zollinger et al. 1999; Livingstone et al. 2002; Schürmann et al. 2007) and 30% following tibial shaft fractures (Sarangi et al. 1993). Following total knee replacement an incidence of 41% at 3 months and 19% at 6 months following surgery has been reported (Stanos et al. 2001). Only one prospective study following distal radial fracture has demonstrated an incidence of 1% or less (Dijkstra et al. 2003). All these

prospective studies have employed a variety of diagnostic criteria including the most up to date IASP tool based on the original work by Bruehl.

The apparent higher rate in most studies probably reflects the transient and often milder nature of the condition in some individuals, the term "community CRPS" has been suggested (Wilson et al. 2005) to represent those individuals who have a either a collection of very mild symptoms, or on initial clinical inspection do not raise any concerns but nevertheless will have signs and symptoms consistent with the diagnosis with careful assessment and if necessary quantitative testing.

The evidence from contemporary retrospective population based studies from North America (Sandroni et al. 2003) and the Netherlands (de Mos et al. 2007) provides interesting yet still controversial data, perhaps underreporting the true incidence of CRPS and exaggerating the proportion of patients that make a relatively quick and full recovery (Bennett et al. 2003). De Mos reported an incidence of 26.2 cases per 100,000 person years, with the highest incidence found in females aged 61 to 70 years old. Fractures accounted for 44% of initiating factors, with the upper limb predominating.

From the prospective experience of CRPS following a distal radial fracture in Bristol, an estimation of the population size (est. 400,000) covered by the Bristol Royal Infirmary and the numbers of distal radial fractures treated per year (approximately 300) using De Mos' figures would in this centre amount to 104 cases of CRPS per year for all causes. Estimating 30% could be attributed to a distal radial fracture would amount to approximately 30 cases of CRPS following distal radial fracture per year (incidence 10%). Therefore suggesting that the population incidence quoted from this study may well be equivalent to those previously reported on by researchers from Bristol.

1.5 CAUSATION

Trauma to an extremity is the commonest precipitating event, accounting for up to 77.6 % of cases (Schwartzman et al. 2009), of the traumatic cases fracture remains the usual precipitant (Veldman et al. 1993; Sandroni et al. 2003; de Mos et al. 2007). A major difficulty in the understanding of this condition has been why one fracture or traumatic insult should give rise to CRPS while an identical fracture or insult in another patient or even in a different limb in the same patient does not. In up to 14% of cases no precipitant insult can be identified (de Boer et al. 2011). Whilst trauma is the commonest precipitant, CRPS is also reported following a wide range of disease processes including: cerebral vascular events (Moskowitz et al. 1958), myocardial ischaemia (Steinbrocker 1947), multiple sclerosis (Schwartzman et al. 2008), brain injury (Gellman et al. 1992), cocaine use (Gay et al. 2000) and herpes zoster infection (Richardson 1954).

1.6 NATURAL HISTORY

The exact onset of CRPS following a precipitating insult is difficult to ascertain. The acute stages of the condition mimic those of acute inflammation, an expected finding in the immediate time period following either trauma or surgery. It is probable that the majority of cases begin within a month after the initial insult, with some cases apparent as early one week following a distal radial fracture (Field et al. 1997). A minority report the onset of some cases are delayed by up to several months, however this questions the relevance of the reported initial insult (Veldman et al. 1993).

The clinical course and severity following onset is varied, reflected by the reported lower incidence following trauma in studies involving established cases. Although most cases resolve within a year (Bickerstaff 1990), some features, particularly stiffness, remain suggesting CRPS may be responsible for significant long-term morbidity even when mild (Field et al. 1992).

In a detailed quality of life study of thirty-one patients with CRPS for a mean duration of 3.3 years, 80% of patients reported significant sleep disturbance and the majority also reported substantial interference scores in nine out of ten points on the modified brief pain inventory quality of life assessment tool (Galer et al. 2000). A more recent retrospective review of six hundred and fifty-six CRPS patients reported that 81% of patients had stopped working because of pain following disease onset. Of this group only 27% had been able to return to work (Schwartzman et al. 2009).

1.7 THE DIAGNOSTIC CONUNDRUM

The ultimate goal amongst researchers and clinicians alike has been the discovery of a single diagnostic test that allows the disease to be sensitively and specifically identified from the extensive list of conditions that share its clinical features. In the acute stages of recovery from limb trauma this is a particular problem because of the extensive cross over with the symptoms and signs of the physiologically normal process of inflammation leading to tissue repair and generation. This goal will almost certainly remain unattainable due to the now widely excepted variability in the conditions clinical course, possibly more than one underlying

pathophysiological causative mechanism and perhaps the existence of more than one disease process occurring under the umbrella of the CRPS label.

What has been achieved so far is the culmination of a process led by the International Association for the Study of Pain (IASP) which sort to standardize diagnostic criteria and taxonomy amongst researchers, improve clinical communication and allow comparison of results from different centres (Harden et al. 2001). This process began with a consensus symposia at Schloss Rettershof in 1988, followed on by a final definitive international workshop in Orlando, Florida in 1993 leading to this group's publication on the taxonomy and criteria of CRPS (table 2). Specifically the consensus agreed not only on what was considered to be the clinical hallmarks essential for diagnosis but also those features previously thought definitive but deemed to be lacking in scientific support such as motor dysfunction, sympathetically mediated pain and osteoporosis. From the outset the goals were not to produce the finished definitive article but to provide a framework that would evolve by way of systematic testing, fine-tuning and validation.

Table 2 IASP diagnostic criteria for CRPS

1) The presence of an initiating noxious event, or a cause of immobilisation.
2) Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.
3) Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.
4) This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

The challenge of moving these diagnostic criteria forward has not been without issue. The original IASP criteria were intended to be broad and sensitive and more recent work has confirmed a lack of specificity, which inevitably leads potentially to over diagnosis and unnecessary or incorrect treatment. Therefore when applied to a heterogeneous group of patients in the pain clinic setting, those with CRPS will be correctly identified, but incorrectly identified with CRPS will be those suffering not from CRPS but a variety other neuropathic entities such as diabetic peripheral neuropathy and radiculopathy. There are two main reasons for this. Firstly the grouping together of distinct elements of the condition into one required criterion, namely oedema, vasomotor and sudomotor dysfunction, compounded by the fact that these maybe self reported at anytime and do not have to be present at the time of assessment. Secondly is the lack of consideration of motor and trophic changes which whilst not essential may aid differentiation from other neuropathic conditions.

The challenge of improving the accuracy of diagnosis, in order to maintain the near perfect sensitivity but greatly improve the specificity of the original IASP criteria has been met by use of internal and external validation techniques.

Internal validation by factor analysis is a statistical method for identifying linked variables within a dataset, in the case of CRPS diagnosis this amounts to the various signs and symptoms that are the distinguishing features of the clinical syndrome. By statistically grouping related variables together researchers have identified that four statistically distinct essential subgroups for CRPS diagnosis exist based on the analysis of one hundred and twenty-three patients diagnosed with CRPS according to the 1993 IASP diagnostic criteria (Harden et al. 1999).

The fourth group contains those features originally not included in the 1993 IASP diagnostic criteria, but now believed to be as important as the other groups, forming a statistically distinct group with no significant overlap with the other three subgroups. This research group have also concluded differentiation between clinical symptoms and signs further improved the diagnostic specificity. From the same patient group cluster analysis of the symptom/sign subgroups in relation to duration of CRPS has shed doubt on the previously described theorem of three distinct sequential stages involved in the evolution of the disorder (De Takats 1937) (Steinbrocker 1947).

Stage 1: Early acute phase characterised by pain and sensory dysfunction, vasomotor disorder, oedema and excessive sweating. This phase may be short or last up to 3 months.

Stage 2: Dystrophic phase characterised by increasing pain and sensory dysfunction, continued vasomotor disorder and the onset of motor and trophic changes.

Stage 3: Atrophic phase characterised by decreasing pain and sensory dysfunction, continued vasomotor disorder and marked motor and trophic changes with joint stiffness due to contractures.

Cluster analysis is a pattern recognition tool that enables patients with a similar subset of symptoms to be grouped together. Grouping patients and correlating the overall duration of CRPS symptoms allowed comparison to the classical three stages model. The results of the cluster analysis were mixed; increased duration of CRPS did in deed correlate with the presence of sensory dysfunction, and a

decreasing likelihood of sweating or oedema abnormalities. However the presence of motor and trophic changes did not correlate with duration of symptoms that contradicts the expected findings in Stage 3 of the classical stages theorem.

The other requirement of a validation process is that of external testing, can the criteria distinguish between CRPS and patients diagnosed with other neuropathic pain conditions? The preliminary report by Galer and colleagues demonstrated that applying the 1993 IASP criteria resulted in a diagnosis of CRPS in up to 36.7% of patients suffering instead with a painful diabetic neuropathy (Galer et al. 1998). The same research group has confirmed the limitation of the 1993 IASP diagnostic criteria on a larger population. Assessing a group of one hundred and seventeen patients with CRPS according to the 1993 IASP criteria and forty-three neuropathic pain patients, the 1993 IASP criteria could not discriminate significantly between the two groups. Instead a four subgroup diagnostic model proposed following internal validation and factor analysis that requires the presence of signs and symptoms has demonstrated an increase in diagnostic accuracy. Various combinations of required numbers of symptoms and signs from each factor subgroup were subject to testing, the most specific combination being four of four symptom categories and two of four sign categories to be positive. This yielded a sensitivity of 0.70 and a specificity of 0.94 (Bruehl et al. 1999) (table 3). These new criteria were adopted and recommended to the IASP by a consensus workshop in Budapest in 2003 as a research tool. A separate but linked clinical diagnostic criteria tool has also been proposed with increased sensitivity. This tool differs from the research version by requiring only three positive responses from the four symptom categories. Recently these new criteria have themselves been externally validated amongst a pain clinic population of one hundred and thirteen patients

diagnosed with CRPS according to the 1993 IASP criteria and forty-seven patients with other neuropathic pain conditions. The results of improved specificity with maintenance of an excepted level of sensitivity mirrored those of the earlier study, however the anticipated differences in specificity between the research and clinical criteria were not evident, raising the question of whether two separate tools are indeed needed (Harden et al. 2010).

Table 3 Modified IASP diagnostic criteria for CRPS research

Continuing pain that is disproportionate to any inciting event.

1) Must report at least one *symptom* in each of the following categories:

- ***Sensory***: Reports of hyperaesthesia.
- ***Vasomotor***: Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
- ***Sudomotor/Oedema***: Reports of oedema and/or sweating changes and/or sweating asymmetry.
- ***Motor/trophic***: Reports of decreased range of movement and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin).

2) Must display at least one *sign* in two or more of the following categories:

- ***Sensory***: Evidence of hyperalgesia and/or allodynia.
- ***Vasomotor***: Evidence of temperature asymmetry and or skin colour changes and/or asymmetry.
- ***Sudomotor/Oedema***: Evidence of oedema and/or sweating changes and/or sweating asymmetry.
- ***Motor/Trophic***: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin).

A further benefit of the revised IASP criteria has also been demonstrated by virtue of improved intra observer agreement between clinicians with the new criteria over the original 1993 criteria (de Mos et al. 2007).

There is little evidence to doubt that the evolution of these new criteria will improve patient care and also harmonise future pain focused research into both

CRPS and other perhaps related non-CRPS pain conditions. Whilst these criteria have been shown to be valid within the setting of a pain clinic, their integrity within an orthopaedic fracture clinic remains unknown. Pain clinicians have solace in the knowledge that these criteria will with a considerably powerful degree of accuracy distinguish CRPS from non-CRPS neuropathic pain amongst their clinic population. The orthopaedic surgeon however is faced with the diagnostic dilemma of distinguishing potential CRPS from a number of other commonly encountered conditions in the fracture clinic environment such as infection, stress fractures, mechanical factors following recent surgery, neuropathy and in particular the normal sequelae of the inflammatory cascade and tissue repair and generation. Whilst a number of these differential diagnoses can be eliminated with simple investigations such as serum inflammatory markers and radiological investigations, a significant proportion will not and therefore the possibility of CRPS as a diagnosis will be raised.

1.8 CLINICAL FEATURES

1.8.1 Signs and Symptoms

Rather than the classical model of the typical CRPS patient moving sequentially through three stages of the condition, the widely accepted view is that of a biphasic condition that begins up to a month after the precipitating event. In the acute stage of the condition, the symptoms and signs of regional inflammation affecting an area larger than the site of injury are characteristic (Figure 1). Later this inflammatory picture is replaced by atrophy and contracture (Figure 2).

Figure 1 Early CRPS affecting the right hand, following a distal radial fracture.

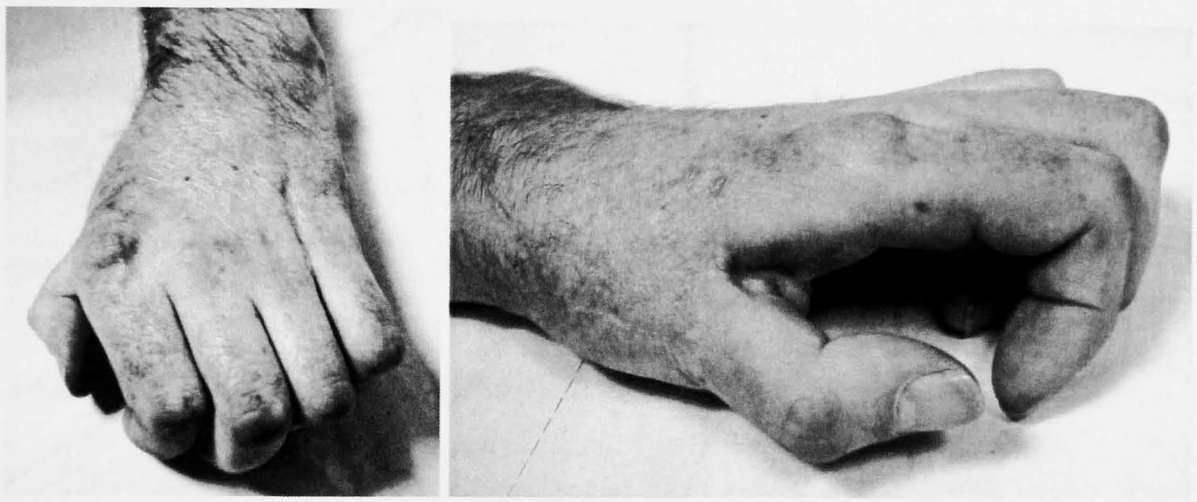


Figure 2 Late CRPS affecting the left hand. (pictures courtesy of Prof. R Atkins)

The condition may spread peripherally and in extreme cases involve the originally unaffected limb (Veldman et al. 1993; Veldman et al. 1996). The pattern of spread maybe contiguous or independent in the ipsilateral limb and mirrored if affecting the contralateral limb (Maleki et al. 2000). Recurrence after a period of remission from most if not all symptoms can occur, 53% of which are spontaneous (Veldman et al. 1996). Whether recurrence is more likely following surgery to the same or differing limb remains unanswered (Dielissen et al. 1995; Zyluk 2004), the

literature lacks any prospective studies perhaps implying that most would agree that surgery in the presence of severe symptoms is risky. Specific management measures taken around the time of surgery such as prophylactic calcitonin, precise surgical technique and early postoperative mobilisation may be important (Marx et al. 2001).

1.8.2 Pain and Sensory Disturbance

Throughout the course of CRPS, the pain experienced is neuropathic. Spontaneous pain, hyperalgesia, allodynia and hyperpathia (table 4) are common but not universal and may not coexist. Pain in the worst examples is unremitting, worsening and may radiate with time. In others it may fluctuate and be affected by environmental changes. It is disproportionate to the precipitating insult.

Table 4 1986 IASP Pain definitions

- ***Pain***: An unpleasant sensory and emotional experience that we primarily associate with tissue damage or describe in terms of tissue damage or both.
- ***Allodynia***: Pain due to a stimulus that does not normally provoke pain.
- ***Hyperaesthesia***: Increased sensitivity to stimulation, excluding special senses.
- ***Hyperalgesia***: An increased response to a stimulus that is normally painful.
- ***Hyperpathia***: Pain characterised by an increased reaction to a stimulus, especially a repetitive one, as well as an increased threshold.

The distribution of pain tends to be distal to the site of injury and is more commonly dorsal when involving the limb (Schwartzman 1993). It is often diffuse and not limited to the territory of a single peripheral nerve, dermatome or neuronal

plexus. Movement, temperature changes, dependent posture, auditory and visual stimuli and emotional upset can all induce a hyperaesthesia (Birklein et al. 2000).

Classical teaching describes the pain as burning in nature, this however this may not be the primary descriptor in many individuals. Sensory pain descriptors rather than affective descriptors predominate such as tearing, stinging, and aching in addition to hot or burning. The majority will localize the pain as deep in the affected limb rather than superficial and the pain tends to be permanent rather than episodic, particularly with increasing disease duration (Birklein et al. 2000; Schwartzman et al. 2009).

Other sensory symptoms such as numbness and paraesthesias are also reported to be common and one study a third of patients had hemisensory impairment as the disturbances of pain and sensory processing (Rommel et al. 1999).

In a questionnaire study of limb neglect symptoms amongst two hundred and twenty-four CRPS patients 84% of responders agreed with at least one cognitive or motor neglect statement (Galer et al. 1999).

1.8.3 Vasomotor Instability, sudomotor activity and oedema

The salient features of an inflammatory process in the early stage of the condition are similar to those due to vasomotor instability (VMI). These include skin colour changes (pink or red), swelling, altered skin temperature and changes in sudomotor function (Figure 3). These symptoms maybe variable and can be related to exercise, painful stimuli and changes in environment. Probably due to combinations of differing and perhaps in part antagonistic pathophysiological mechanisms vasomotor changes are not static (Wasner et al. 2005). In a

prospective study of eight hundred and twenty-nine patients 91% had skin discolouration, 92% had altered skin temperature and 47% had hyperhidrosis. The same study subdivided the acute stage into two distinct groups depending on the temperature difference findings. The longer the duration of symptoms the more likely the finding of cold limb, therefore the terms "warm" and "cold" CRPS were coined (Veldman et al. 1993).

Figure 3 Increased sudomotor function in a foot affected by CRPS. (Picture courtesy of Prof. R Atkins)

Sudomotor dysfunction has been demonstrated under controlled conditions in CRPS subjects to be more likely due to peripheral post ganglion induced sudomotor stimulation or possible increased sweat gland responsiveness rather than a disturbance in the central thermoregulatory mechanism (Birklein et al. 1997b). The neuropeptide calcitonin gene related peptide (CGRP) enhances sweat gland

activity in normal subjects and is implicated in pathomechanisms related to other CRPS features (Schlereth et al. 2006).

Early oedema may be diffuse or localised and was present in 86% of patients examined within two months of onset of symptoms when studied by Veldman prospectively (Veldman et al. 1993). In this study the drop in incidence of oedema compared to duration of symptoms was more marked than those other early symptoms and signs observed such as pain, colour change and temperature difference.

Measurement can be performed simply by either volumetric hand assessment utilising water displacement with the contralateral hand as a surrogate baseline measure, or by limb or digit circumference measurement.

Local oedema is caused in part by tissue fluid extravasation secondary to changes in small blood vessel diameter and vessel wall permeability. These vascular changes are under the influence of a number of neuropeptides released by abnormally activated somatic fibres that in affect can mimic the normal physiological affects of the sympathetic nervous system. This neuronal phenomenon has been artificially exaggerated in CRPS patients by measured increases to local blood flow and protein extravasation following transcutaneous electrical excitation of all classes of C-fibres in the affected CRPS limb in comparison to healthy control subjects (Weber et al. 2001). Other possible mechanisms include alterations to autonomically regulated lymphatic flow (Howarth et al. 1999).

1.8.4 Motor and trophic changes

Motor symptoms are present in the majority of cases and can include tremor, weakness, exaggerated tendon reflexes, dystonia, paresis, akinesia, bradykinesia and myoclonic jerks (Birklein et al. 2000; Schwartzman et al. 2009; Veldman et al. 1993). Joint positioning motor skills are also profoundly affected (Lewis et al. 2010). Originally not included in the 1993 IASP criteria, recent studies have demonstrated their importance to improving the specificity of diagnostic criteria (Bruehl et al. 1999; Harden et al. 1999; Harden et al. 2010).

Limited active range of movement contributes significantly to the disability associated with the disorder both in the acute stages and chronically in the cold atrophic phase. If contractures manifest then these will be difficult to treat. Cosmesis may be of concern to some individuals (Zyluk 2001).

The aetiology of joint stiffness is multifactorial. Early in the disease pain, joint tenderness, oedema, ill-fitting splints joint capsule contracture, collateral ligament shortening and early flexor tendon sheath adhesions may all contribute to the process. (Figure 4).

Articular cartilage of the finger joints has not been implicated in loss of finger movements (Doury et al. 1981). Later in the disease evolution muscle fibrosis and skin contractures will perpetuate the problem.

With a significant number of patients also experiencing disturbances to the motor system that can occur early in the condition, these factors will almost certainly contribute to this feature of the disease.

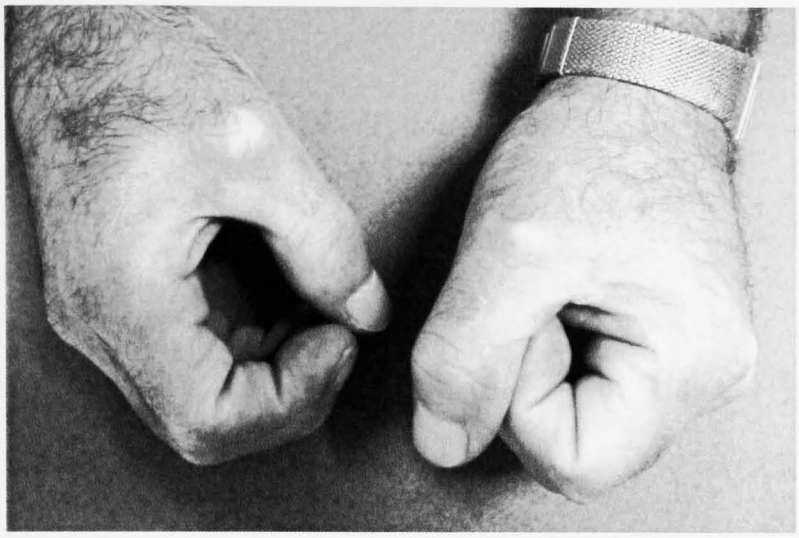


Figure 4 Late onset finger contractures in CRPS (Picture courtesy of Prof. R Atkins)

The skin is thin with joint creases and subcutaneous fat disappearing. Brown-grey scaly pigmentation develops in a high proportion of patients. Hairs become fragile, uneven and curled. Changes in hair growth were observed in 55% of patients in Veldman's prospective series Veldman 1993. Calcitonin gene related peptide, a neuropeptide, implicated in the pathogenesis of CRPS has numerous receptors on in human hairy skin and may be the explanation to this finding (Hagner et al. 2002). Normal finger and toe growth may also be impaired with pitting, ridging, fragility and discolouration. Palmar and plantar fascias can thicken and contract causing Dupuytren's disease (Livingstone et al. 1999).

1.8.5 Regions affected

The upper limb is more commonly affected than the lower (Veldman et al. 1993; de Mos et al. 2007). Distal involvement tends to predominate probably due to the relatively higher occurrence of injuries at the wrist in the general population. When the entire arm is affected the elbow tends to be spared. Patients with distal

upper limb CRPS have a significant incidence of associated shoulder complaints (the so called shoulder-hand syndrome). In most this may be due to a biceps tendonitis. (Veldman et al. 1995). It is probable that a significant proportion of frozen shoulders can be considered a form of CRPS (Steinbrocker 1968). The clinical similarities between the two are supported by changes observed on bone scans and plain radiographs (Müller et al. 2000). CRPS can occur following surgical procedures in the upper limb such as carpel tunnel decompression (whether performed endoscopically or as open procedure), and Dupuytrens release. CRPS affecting the lower limb is recognised following both trauma and surgery. These include tibial fractures, amputations and crush injuries to the foot. As well as the periphery of the lower limb, CRPS and insults to the knee have also been extensively reported on (Katz et al. 1986; Katz et al. 1987; Stanos et al. 2001). Rarely it can complicate pregnancy (Perka et al. 1998; Poncelet et al. 1999). CRPS affecting the face (Melis et al. 2002) and thoracic wall (Rasmussen et al. 2009) have been described.

1.9 PATHOGENESIS

The development of CRPS probably almost certainly involves at least two linked pathophysiological processes, one occurring at the site of the injury, involving local soft tissues and the peripheral nervous system. The second occurring in the central nervous system leading to altered reflexes and neuronal pathways. A number of theories have been investigated and discussed (Figure 5):

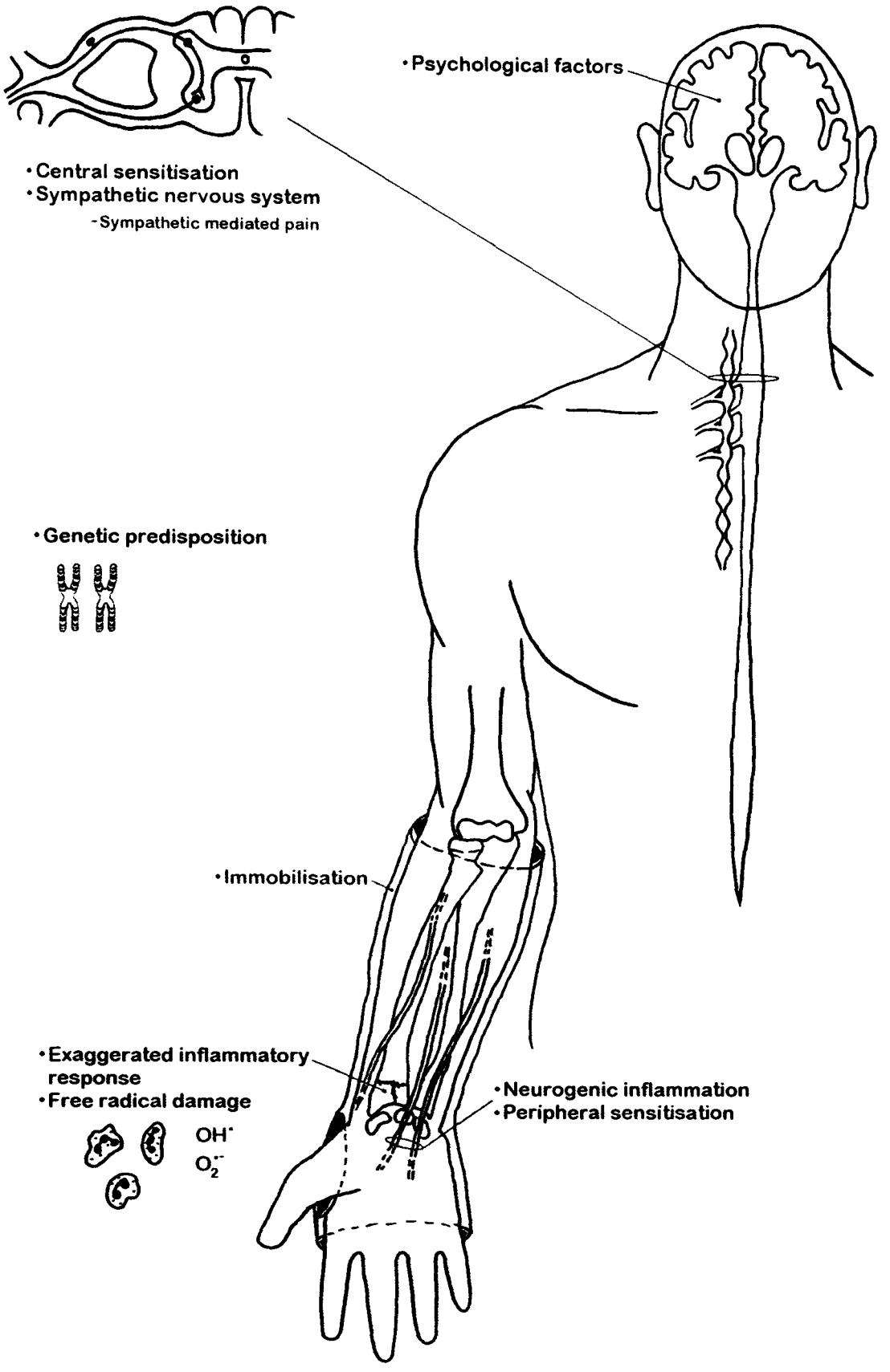


Figure 5 Proposed mechanisms involved in the development of CRPS.

1.9.1 Genetic predisposition

Evidence for an inherited component to the development of neuropathic pain has been described in both animal and human studies. Support for inherited forms of CRPS arises both from studies of familial prevalence and searches for linked genetic factors by human genomic analysis.

Familial CRPS occurrence has been described in thirty-one families with between two and five affected members. Although a clear pattern of inheritance was not identified, familial cases of CRPS tended to be more severe and occur at a younger age in comparison to individuals with sporadic CRPS (de Rooij et al 2009). The condition has been linked to certain variations (polymorphisms) of genes encoding angiotensin-converting enzyme (ACE) and human leukocyte antigen (HLA) class I and II molecules (Mailis et al. 1994; de Rooij et al. 2009). These genes have a high amount of variation and, as they are inherited in a Mendelian fashion, can be useful as genetic markers of disease but may also be linked to disease severity, progression or phenotype. Of note is that ACE helps to degrade neuropeptides linked with neurogenic inflammation such as bradykinin and a small study of CRPS patients found a greater prevalence of genetic anomalies in the ACE gene compared to controls (de Mos et al. 2009). This observation has however been challenged by other investigators (Hühne et al. 2004).

In the first prospective examination for genetic factors in patients at risk of developing CRPS following a distal radial fracture an increase in the prevalence of a known polymorphism for the gene encoding the α_{1a}-adrenoceptor I was identified in those patients who developed CRPS according to the Bruehl criteria. Other known polymorphisms for genes encoding ACE, interleukins, TNFα, transforming

growth factor β, tachykinin and its receptor, calcitonin gene-related peptide, and neuropeptide Y were found not to be more prevalent in the CRPS group (Herlyn et al. 2010).

1.9.2 Sympathetic nervous system abnormalities

The diagnosis of CRPS is dependent on the presence of the symptoms and signs of vasomotor instability and trophic changes suggesting sympathetic nervous system (SNS) dysfunction. Although the SNS is not normally active in the processing and transmission of noxious stimuli in some cases of CRPS the phenomenon of sympathetically maintained pain (SMP) exists (Stanton-Hicks et al. 1995). SMP maybe relieved by stellate ganglion block to the affected limb (Price et al. 1998) and then restored by norepinephrine injection (Torebjörk et al. 1995). In CRPS patients diagnosed with SMP it has been demonstrated that administering intradermal norepinephrine at physiological concentrations evokes greater pain in the affected limb than in the contralateral limb or in control subjects (Ali et al. 2000). Further evidence arises from the observations that increasing sympathetic activity worsens spontaneous pain, mechanical allodynia (Jänig 2001) and thermal hyperalgesia (Drummond et al. 2001) in CRPS patients.

The development of norepinephrine-evoked pain may however be time dependent and did not affect patients with early acute CRPS in one study (Birklein et al. 1997a). This finding may well explain why intra venous regional sympathetic blockade with guanethidine, traditionally a mainstay of treatment in resistant cases, does not improve the symptoms or alter the natural history of CRPS following a distal radial fracture (Livingstone et al. 2002).

The mechanism by which the SNS may be involved in CRPS pain is not clear. Adrenergic supersensitivity in the affected limb may explain this in a number of ways. The density of α_1 adrenoceptors is increased in the non-vascular epidermal tissue of symptomatic limbs, following partial nerve injury, when both injured and uninjured somatic axons start to express α_1 adrenoceptors (Davis et al. 1991; Drummond et al. 1996). Cutaneous vasculature shows increased responsiveness to noradrenalin in limbs of CRPS patients (Arnold et al. 1993). Thus adrenergic supersensitivity could lead to sympathetic over activity causing the sensitisation of the somatic sensory nervous system to circulating catecholamines and noradrenalin released from post-ganglionic sympathetic terminals. Adrenergic supersensitivity may cause vasoconstriction, aggravating tissue inflammation, causing a build up of nociceptive mediators produced during the inflammatory process. Alternatively adrenergic supersensitivity might interfere with the normal production of mediators such as nerve growth factor (NGF). α_1 adrenergic activity increases the secretion of NGF, an inflammatory mediator known to stimulate the growth of nociceptive afferents and to cause the release of nociceptive mediators from mast cells, sympathetic neurones and macrophages (Tuttle et al. 1993). Increased α_2 adrenergic activity in the SNS stimulates the synthesis of prostaglandins E and I both potent in increasing the excitability of nociceptive afferent nerve fibres (Gonzales et al. 1991).

1.9.3 Peripheral Sensitisation

Changes in normal neuronal functioning, leading to pain hypersensitivity, including allodynia has been attributed to neuronal plasticity. This physiological process is

an ongoing phenomenon that reflects changes in neuronal environment and activity (Woolf et al. 2000). The experience of pain occurs when small fibre nociceptors (C and Aδ fibres in the skin) are stimulated. These fibres normally require significant energy and hence a stimulus that is tissue threatening or damaging for a pain to be felt. These fibres are however activity dependent and if stimulated at low intensity the perception is crude touch.

If the stimulus is repetitive and potentially threatening these nociceptors can become sensitised, decreasing their threshold to fire. This is a normal adaptive physiological response to injury. Unfortunately this response can become harmful when the threatening environment recedes but the nociceptors remain sensitised. This pathophysiological state is further compounded by the fact that these small fibres proliferate in response to the pro-inflammatory soup of cytokines, neurotransmitters and growth factors that are released locally during the initial injury phase.

Histological studies of peripheral nerves from patients with CRPS (type 1) have shown normal efferent nerve fibres but abnormal C-nociceptive fibres (van der Laan et al. 1998b).

A combination of activity dependent firing, an adaptive response to a repeated stimulus and proliferation in response to an injury environment leads to a vicious circle of continuing pain without a noxious stimulus present.

1.9.4 Central processing changes

The unexplained pain of CRPS has been linked to central sensitisation. Following nerve injury, both injured and non-injured sensory afferents can fire

spontaneously. Prolonged input to the dorsal horn as a result of spontaneous firing in C fibre nociceptors sensitises dorsal horn neurons so that they abnormally respond to innocuous inputs, this may lead to an exaggerated dorsal horn response to A-fibre input and thus allodynia. Peripheral nerve injury may also reduce the affect of central descending inhibitory pathways. The spread of pain beyond the territory of an affected nerve can be reversed by certain receptor antagonists implicated in central sensitisation (Woolf et al. 1999).

1.9.5 Fracture management

The incidence of CRPS following tibial shaft fracture is not affected by the method of fracture management employed (Sarangi et al. 1993). The initial degree of fracture displacement, a surrogate marker of injury severity, is linked statistically to the development of CRPS (Livingstone 2000) along with increasing Frykman grade and ulnar styloid involvement (Bickerstaff et al. 1994). The method of anaesthetic employed for initial fracture reduction, the quality of reduction and the need for further manipulations following distal radial fracture does not appear to be influential (Atkins et al. 1990; (Livingstone 2000). Excessive plaster of Paris cast tightness has been linked to the development of CRPS following distal radial fracture (Field et al. 1994). Immobilisation has been proposed to cause a "neglect-like" phenomenon in which the patients find difficulty in initiating movement or accurately directing it (Galer et al. 2001). Learned pain avoidance behaviour in response to allodynia may exacerbate changes of disuse since normal tactile and proprioceptive input are necessary for correct central nerve signal processing. Indeed, it has been suggested that abnormal mobility is the entire cause, due to loss

of integration between sensory input and motor output (Harris 1999; McCabe et al. 2003).

1.9.6 Psychological factors

Some physicians may feel that the complex array of symptoms, the seemly innocuous "minor trauma" preceding the onset (or in deed lack of trauma) and the lack of conclusive diagnostic test or imaging points to CRPS being primarily of psychological origin. This concept, however, is unsupported (Bruehl 2001).

Although several studies have linked certain psychological factors with CRPS including emotional lability, low pain threshold, hysteria, depression and antecedent psychological stress, most CRPS patients are normal (Vincent et al. 1982). One proposed theory is that of a complex interaction between the, now apparent, pathophysiological models for the disease and certain psychological processes to explain the progression and longevity seen in certain patients. (Bruehl et al. 1996).

1.9.7 Exaggerated inflammatory response and free radicals

In the acute stages of CRPS the condition demonstrates all the classical symptoms and signs of inflammation: rubor, calor, dolor, tumor and functio laesa (Veldman et al. 1993). Sudeck first postulated that an exaggerated inflammatory response could contribute to the aetiology of the condition he described in 1900. Over the last three decades this theory has been revived and investigated.

A number of clinical studies indicate that CRPS patients display significant increases in the pro-inflammatory cytokines TNF-α and interleukins -1β, -2, and -6

in local blister fluid, circulating plasma, and cerebrospinal fluid (Huygen et al. 2002; Alexander et al. 2005; Wesseldijk et al. 2008; Krämer et al. 2011) and decreases in the plasma levels of the anti-inflammatory cytokines interleukins -4 and -10 (Uçeyler et al. 2007). One source of these locally derived inflammatory mediators in the skin are activated keratinocytes (Li et al. 2010).

Using Indium-111 labelled human non-specific polyclonal immunoglobulin G (In-111-IgG) as a macromolecule and scintigraphy, a significant increase in blood flow and accumulation of In-111-IgG in the affected hand was identified in patients with upper limb CRPS. This observation was reduced in the subgroup of patients included with a diagnosis of CRPS for greater than five months implying that a transient increase in vascular permeability occurs early in the disease, indicating an inflammatory process (Oyen et al. 1993).

In a small study of six CRPS patients compared to control subjects with a distal radial fracture a significant difference in the accumulation of radiolabeled autologous leukocytes in the affected hands of the CRPS group at a mean of seventy-one days post injury or surgery was observed suggesting an ongoing inflammatory response (Tan et al. 2005).

It has been known for some time that leukocytes are a source of reactive oxygen species or free radicals (Babior et al. 1973) and tissue damage following acute inflammatory processes is caused in part by free radical deposition (Ward et al. 1983; Fantone et al. 1982). Evidence for the involvement of free radicals in the development of the CRPS has been reported by a number of researchers.

An animal model has demonstrated a CRPS-like limb following infusion of the free radical donor tert-butylhydroperoxide directly into the hind limb of a rat.

Significant differences in comparison to a control group of animals injected with saline were observed with respect to skin temperature, limb volume, the presence of erythema, impaired limb function and pain assessment by observation. Histological analysis of the hind limb musculature 24 hours after infusion showed cellular degeneration, oedema and leukocyte infiltration (van der Laan et al. 1998a). Amputated human specimens affected by CRPS show basement membrane thickening consistent with overexposure to free radicals (van der Laan et al. 1998b) and mitochondrial dysfunction in end stage CRPS (Tan et al. 2011). Maternally inherited disorders of mitochondrial dysfunction have also been linked to the development of CRPS in children (Higashimoto et al. 2008).

Salivary markers of oxidative stress are increased in CRPS patients when compared to controls, a finding that may be a useful non-invasive way to monitor future treatments (Eisenberg et al. 2008).

In another recently reported animal study, a chronic post-ischaemia pain (CPIP) model in a rat has created CRPS-like limb following prolonged ischaemia with a tourniquet (Coderre et al. 2004). Whilst the larger neurological structures close to the tourniquet do not show signs of injury under detailed microscopic assessment, smaller cutaneous nerve ending density in the injured limb is decreased. Also observed is the presence of microvascular pathology in the digital nerves and limb musculature. This model, in support of an inflammatory process, has demonstrated an early rise in the measured local levels of the pro-inflammatory cytokines; tumour necrosis factor alpha, interleukin-1 and interleukin-6, and the related transcription factor, nuclear factor kappa B in the rat limb soon after the development of CRPS-like symptoms.

In addition Malondialdehyde, a product of free radical-induced lipid peroxidation, is significantly elevated. With the introduction of free radical scavengers, hind limb allodynia can be ameliorated, suggesting a key role of free radicals (Laferrière et al. 2008). This model has led the researchers theorise that the observed early inflammatory response to an ischaemia-reperfusion injury produces a form of self perpetuating sub acute compartment syndrome that impairs capillary blood flow to muscle, nerve, and bone by a "slow-flow/no-reflow" phenomenon (Coderre et al. 2010).

In an animal model nitric oxide significantly increases the excitatory neuropeptide Substance P release from the peripheral endings of small diameter primary afferent neurones (Yonehara et al. 1999). Substance P has been implicated in CRPS via the process of neurogenic inflammation. Increased nitric oxide release from the leukocytes derived from CRPS patients has been shown following in vitro stimulation by the cytokines interleukin-1b and interferon-g (Hartrick 2002).

1.9.8 Free Radicals and Smoking

Tobacco smoke is made up of a complex mixture of chemicals including a large number known to be free radicals. These compounds exist both in the solid tar phase and the gas smoke phase and most have a long half life (Valavanidis et al. 2009). As well as containing free radicals, tobacco smoke increases the oxidative metabolism of leukocytes, a process that in itself releases further free radicals such as superoxide, hydrogen peroxide and hydroxyl radicals (Ludwig et al. 1982). Depletion of antioxidant levels such as ascorbic acid is known to occur in smokers and those exposed to passive smoking (Tribble et al. 1993; Lykkesfeldt et al. 1997).

This is due in part to an increased utilization of ascorbic acid to buffer the increased levels of free radicals but also may be due to decreased dietary in take when compared to non-smokers (Tribble et al. 1993).

The role of smoking in the pathogenesis of CRPS has not extensively investigated and the few reports available are conflicting. An et al from Ohio observed in a retrospective study on fifty-three consecutive CRPS patients an increase in the prevalence of current active smoking at the time of diagnosis when compared to a cohort of control patients made up from hospitalized patients without CRPS (68% vs. 37%) (An et al 1988). More recently retrospectively reviewed data from a larger cohort of six hundred and fifty-six patients from Philadelphia diagnosed with CRPS recorded a prevalence of smoking at the time of diagnosis of approximately 50% (Schwartzman et al. 2009). These figures would suggest smoking is a factor given the national prevalence of smoking in North America at the time of these reports was around 30% and 20% respectively (www.cdc.gov). In contrast a prospective study of one hundred and fourteen patients with a distal radial fracture found no link between the development of CRPS and a smoking history (Goris et al. 2007).

1.9.9 Neurogenic Inflammation

Stimulation by increased cytokine activity maintains a nociceptors reaction to an injury by a process called neurogenic inflammation. During this process neuropeptides including substance P, calcitonin gene-related peptide (CGRP) and somatostatin are released from neurones. Peripherally neuropeptides contribute to changes in vascular permeability whilst centrally they have an excitatory affect.

In 1931 von Euler and Gaddum described a tissue extract, preparation P, that they noted caused intestinal contraction and vasodilatation. This was a novel substance compared to known vasodilators such as histamine, choline, adenosine and kallikrein by virtue of its differing chemical and physical properties (V Euler et al. 1931).

Substance P is a member of the Tachykinin family of neuropeptides along with neurokinins A and B and neuropeptides K and γ. It is synthesised predominately in type B cells of the dorsal root ganglion in response to stimulation of primary afferent nociceptive C fibres. Of the three associated receptor subtypes so far identified, Substance P has the greatest affinity for the neurokinin-1 (NK-1) subtype (Cascieri et al. 1992).

Substance P is widely distributed within primary sensory neurones throughout the body, but predominately within the central and peripheral nervous systems. The mapping of the distribution of NK-1 receptor subtypes has also revealed its abundance in bone (Goto et al. 1998). With this knowledge and a myriad of in vitro an in vivo studies Substance P has been linked with a variety of physiological and pathological actions including pain transmission, neurogenic inflammation, smooth muscle contraction, vasodilatation and modulation of bone cell function.

Due to its involvement with these processes, Substance P has been investigated with respect to the underlying pathophysiology of CRPS. Blair et al observed that serum levels of a number of different neuropeptides including CGRP, bradykinin, and vasoactive intestinal peptide (VIP), but not Substance P were raised in CRPS patients (Blair et al. 1998). Leis et al demonstrated an increase in plasma protein extravasation following a subdermal injection of Substance P into the skin of CRPS patients when compared to control subjects in both their affected and unaffected

limbs (Leis et al. 2003). Demonstrating this process occurring in the unaffected limb supports the theory of an underlying predisposition, either an increased natural density of NK-1 receptors or an impairment of deactivation of Substance P. Facilitated neurogenic inflammation by artificial exaggeration in CRPS increases local blood flow and protein extravasation following transcutaneous electrical excitation of all classes of C-fibres in the affected CRPS limb in comparison to healthy control subjects (Weber et al. 2001). This process however appears not be present in the unaffected limbs of CRPS patients implying an initiating event is required to up regulate neuropeptide synthesis and transmission (Leis et al. 2004). Infusion of exogenous substance P into an extremity mimics the signs and symptoms of CRPS in a rat model (Gradl et al. 2007) and intrathecal injection in another rat model causes thermal hyperalgesia along with release of excitatory amino acids and prostaglandin E_2 (Hua et al. 1999). Other groups have postulated that a defect in neuropeptide enzymatic breakdown may play a role, a theory supported by the observation of the measured effects of an induced neurogenic inflammation in healthy subjects following percutaneous infusion of phosphoramidon, a neuroendopeptidase inhibitor (Krämer et al. 2005).

In some CRPS patients it appears glucocorticoids can be beneficial (Braus et al. 1994) (Christensen et al. 1982). This evidence has found support from an animal model of CRPS (type 2) whereby neurogenic extravasation and mechanical and thermal hyperalgesia were reversed following a continuous infusion of methylprednisolone (Kingery et al. 2001a; Kingery et al. 2001b). Under similar conditions a substance P receptor antagonist reverses the extravasation, warmth and oedema seen (Kingery et al. 2003). A major breakthrough was made by the same group when they demonstrated similar results with a substance P antagonist

and glucocorticoids in a closed tibial fracture rat model, the closest model yet to CRPS (type 1) in humans (Guo et al. 2004). Of interest in the same study was the fact that in some control rats who were immobilised but not injured a temporary CRPS-like syndrome developed, in keeping with findings observed in healthy human volunteers (Butler 2001).

An understanding of the effects of Substance P on osteoblasts, osteoclasts and their derivative cell precursors may explain the associated bony changes seen on both simple radiographs and bone scintigraphy. Periarticular patchy osteoporosis and the generalised uptake on the delayed phases of scintigraphy have been noted by several authors and subject to a variety of theories.

Normal bone turnover is a complicated and not fully understood process, controlled by a number of factors. Neuropeptide signalling is one such factor and has been subject to extensive research. Conflicting reports exist on both the presence of Substance P NK-1 receptors in bone and bone cells and the effect of Substance P on cellular activity and function within bone. There appears to be an important role for Substance P in both bone formation and resorption.

Some authors report an increase in mature osteoblast numbers as well as protein production and mineralisation whilst others report an inhibitory effect on alkaline phosphatase activity, mineralisation and osteoblastic gene expression in the presence of Substance P (Liu et al. 2007). These differences may be due to the time dependent expression of the NK-1 receptor as suggested by more recent studies supporting the stimulatory theory (Goto et al. 2007; Wang et al. 2009).

Substance P is involved in bone resorption, it has a stimulatory affect on osteoclast numbers and activity probably via activation of Nuclear factor kappa B (NF-κB), a

protein that controls the transcription of DNA (Sohn 2005). It may also have indirect effects on resorption by increasing inflammatory cytokine levels such as IL-1, IL-6 and TNF-α, all of which stimulate osteoclastic activity (Liu et al. 2007). Substance P therefore has the ability to stimulate bone formation and resorption, a difference almost certainly dependent on dose and an observation that might contribute to the mechanisms causing the bone density changes found not only in CRPS but other chronic disease states such as rheumatoid arthritis and osteoporosis.

1.10 ANTIOXIDANTS AND COMPLEX REGIONAL PAIN SYNDROME TREATMENT

In 1985 Goris began the revival of a theme first muted by Südeck on the role of exaggerated inflammation in the pathogenesis of CRPS. The addition of a hypothesis of continued toxic free radical production leading to widespread tissue damage was suggested (Goris 1985). Earlier separate studies by Fantone and Ward had demonstrated the production of toxic oxygen free radicals by activated phagocytes during the inflammatory response and their potential to damage normal healthy tissue in the process.

The first pilot study by Goris et al of the effect of the antioxidant free radical scavengers dimethyl sulfoxide (DMSO) and mannitol on nine CRPS patients was followed by a cross over study on twenty patients comparing topically applied 50% DMSO with placebo over a total trial period of fourteen days. The duration of symptoms was two months or less in twelve patients diagnosed with CRPS using a

predecessor of the Veldman criteria (Veldman 1993) (Table 6). The results were encouraging with overall subjective improvements being assessed in fifteen patients by the patients themselves and researchers alike. Objective measurements were not utilised. The researchers concluded that the earlier the diagnosis of CRPS the more likely the success of this treatment (Goris et al. 1987). Similar results have been reported by other studies, all carried out in the Netherlands (Zuurmond et al. 1996; Perez et al. 2003; Geertzen et al. 1994; Langendijk et al. 1993). The treatment however has not gained significant popularity outside the Netherlands and indeed these results have yet to be repeated in any other country.

Other basic science studies and animal model work have supported the free radical theory as mentioned previously.

Table 5 Veldman criteria for the diagnosis of CRPS.

1. Four out of five signs or symptoms present from:-
• *Unexplained diffuse pain*
• *Difference in skin colour relative to other limb*
• *Diffuse oedema*
• *Difference in skin temperature relative to other limb*
• *Limited active range of motion*
2. Occurrence or increase of above signs or symptoms after use
3. Above signs and symptoms present in an area larger than the area of primary injury or operation and including an area distal to the primary injury

1.11 ANTIOXIDANTS AND THE PREVENTION OF COMPLEX REGIONAL PAIN SYNDROME

Zollinger first reported the use of an antioxidant for the prevention of CRPS following distal radial fracture in 1999. A prospective randomised double-blinded trial compared the efficacy of 500mg of ascorbic acid to placebo. CRPS was diagnosed according to the Veldman criteria. A per protocol analysis of the one hundred and fifteen patients after patient exclusions demonstrated an prevalence of 22% in the placebo group and 7% in the ascorbic acid group (Relative risk 2.91) (Zollinger et al. 1999).

The same group followed this report with a prospective randomised double-blinded dose response study, reporting again a statistically significant difference in the overall prevalence of CRPS between the ascorbic acid groups and the placebo group (2.4% vs. 10.1% p=0.002). Significance was observed between the two groups at a dosage of 500mg or 1000mg. At a dosing of 200mg the difference in prevalence was not statistically significant. The diagnosis of CRPS was again based on the Veldman criteria (Zollinger et al. 2007).

Other retrospective studies using a mixture of diagnostic criteria and investigations have also supported the use of ascorbic acid in the prevention of CRPS in operative stabilisation of distal radial fractures (Cazeneuve et al. 2002), foot and ankle surgery (Besse et al. 2009) and 1st carpometacarpal joint replacement surgery (Zollinger et al. 2010).

1.12 ASCORBIC ACID AND ANTIOXIDANT THERAPY

An antioxidant is any substance that delays, prevents or removes oxidative damage to a target molecule. Antioxidants can be complex molecules such as the superoxide dismutases, catalases and peroxiredoxins, or simpler ones such as uric acid, glutathione and ascorbic acid (Gutteridge et al. 2010)

Two groups in North America and Hungary discovered the water-soluble antioxidant ascorbic acid in 1932 (King et al. 1932; Svirbely et al. 1932). The following year its structure was identified and in the same period its first successful synthesis (Haworth et al. 1933).

These events were the accumulation of centuries of experience with the disastrous consequences of scurvy in a wide variety of settings including long distance sea and land exploration, new world colonisation, famine and war. The first probable reports of a condition resembling scurvy can be traced to 1500 B.C. As early as 1227 Gilbertus de Aquila recognized a condition seen previously on a voyage to Palestine and accordingly advised future voyagers to carry ample supplies of fruit and vegetables. The first appearance of the term scurvy in an English publication was not until 1589 by Richard Hakluyt following a nautical expedition (Sauberlich 1997).

Despite early accounts of effective means to avoid scurvy it was not until the 18th century that the benefits of antiscorbutics such as lemon juice, nettle juice and scurvy grass were widespread amongst explorers. One individual to help promote the benefits of citrus fruits against the outbreak of scurvy was James Lind who published the findings of what is commonly regarded as the world's first controlled trial in clinical science in 1753, "A Treatise of the Scurvy" (Krehl 1953).

Ascorbic acid is vital for a number of biological pathways, including its role as an electron donor to a number of enzymes that are required for functions such as amino acid hydroxylation to ensure collagen structural normality and the production of norepinephrine from dopamine. It has both antioxidant and in the correct environment pro oxidant capabilities, although the relevance of this finding in vivo remains controversial (Carr et al. 1999). It is thought to be important in the prevention of diseases associated with the phenomenon of oxidative stress whereby reactive oxygen species or free radicals build up as a by-product of many physiological or pathophysiological processes. These highly reactive chemicals inflict damage on cellular structures via damage to DNA and oxidation of enzymes, amino acids and fatty acids (lipid peroxidation). Whilst most animals and plants are capable of ascorbic acid synthesis from either glucose or galactose, humans are not due to a presumed evolutionary loss of the enzyme L-gulonolactone oxidase, a trait they share with monkeys, guinea pigs and fruit bats. Diet is therefore the only source of ascorbic acid in these species (Burri et al. 1997).

The precise role of ascorbic acid in the immune system is not fully understood. As a requirement of normal cellular function, a large concentration exists within leukocytes, which rapidly declines during infection and stress and can be lowered in chronic diseases (Lunec et al. 1985), ageing (Milne et al. 1971; Garry et al. 1987) and as a result of smoking (Brook et al. 1968). Ascorbic acid deficiency in vivo effects normal leukocyte biology by a number of proposed mechanisms including cellular apoptosis (Vissers et al. 2007). Supplementation of ascorbic acid has demonstrated both in vitro and in vivo to improve leukocyte function (Goetzl et al.

1974) and reduce leukocyte free radical production (Herbaczyńska-Cedro et al. 1994).

Since its discovery ascorbic acid has been the subject of much interest, debate and optimism amongst the health and scientific community as to its potential benefits to human society. Thousands of trials have been carried out and whilst some benefits have been stated, numerous trials and meta analyses have not reached the same conclusions (Bjelakovic et al. 2008).

Debate still surrounds what is considered to be the recommended daily allowance (RDA) for optimising health. As little as 10 mg per day will prevent the onset of scurvy, yet the RDA is 75mg per day for females and 90mg per day for males. Others have reported that in order to reach a plasma saturation concentration of 70mmol/l; an RDA of 200mg is required (Lykkesfeldt et al. 2010).

Considering the volumes of studies carried out to ascertain the benefits of ascorbic acid in the treatment and prevention of diseases such as cancer, cardiovascular diseases and respiratory diseases, the literature on the use of antioxidants for the treatment or prevention of conditions associated with the disciplines of pain medicine and trauma and orthopaedics are relatively sparse.

Neuropathic pain models in animals have shown some potential in the efficacy of antioxidants. Kim reported on the significant improvement of mechanical allodynia following Vitamin E administration at three days after L5 spinal nerve root ligation in a rat model (Kim et al. 2006). In another neuropathic rat model the role of animal age and early and late intervention with the antioxidant tirilazad on thermal hyperalgesia was investigated. The study revealed a significant delay in recovery of

thermal hyperalgesia in older animals compared to young. Biochemical markers of oxidative stress were also raised in both age groups however the elderly rats had significantly higher levels of markers than their younger counterparts. Another arm of this study demonstrated that the administration of the long acting antioxidant tirilazad to the study group as a whole alleviated thermal hyperalgesia when given seven days after nerve ligation. Earlier intervention before seven days with this treatment showed no benefit (Khalil et al. 2001). An animal model investigating the role of ascorbic acid in free radical associated neuropathic pain has not been reported thus far.

A beneficial effect on muscle function and reduction of inflammatory mediated tissue changes and damage has been observed in animal models of ischaemia-reperfusion and compartment syndrome with pre-treatment of ascorbic acid (Kearns et al. 2001; Kearns et al. 2004). Work on fracture healing in animals has demonstrated the beneficial effects of ascorbic acid on accelerating fracture healing (Sarisozen et al. 2002) and improving the mechanical properties of fracture callus (Alcantara-Martos et al. 2007). The protective effects of ascorbic acid on fracture healing in rats treated with a free radical donor have also been demonstrated (Duygulu et al. 2007).

The prospective studies reported by Zollinger on CRPS prevention with ascorbic acid were partly devised as a result of the benefits of ascorbic acid in burns by reducing microvascular leakage of fluid and protein and therefore reducing the volume of fluid resuscitation required (Matsuda et al. 1992; Tanaka et al. 2000). Since Zollinger's studies no other prospective randomised control trials on the benefits of ascorbic acid in CRPS prevention have been published and in fact more has been published on the concerns of his trial methodology (Amadio 2000; Frölke

2007; Rogers et al. 2008; Rohekar 2008), with particular reference to the diagnostic criteria, an issue raised by the research group in their conclusion (Zollinger et al. 2007).

With such a compelling array of evidence from a variety of human, animal and in vitro studies exploring the role of free radicals in the pathogenesis of CRPS, the potential benefits of antioxidant treatment to reduce or indeed prevent CRPS requires further clinical assessment.

Confirmation of its usefulness would provide an inexpensive, safe and well-tolerated means of preventing a condition that can cause extreme disability, anguish and pain for sufferers and a financial burden to society as a whole.

The study is divided into two pillars. The first pillar aim is to validate a set of previously utilised diagnostic criteria for confirmation of prospectively studied CRPS following distal radial fracture with the most up to date research diagnostic criteria as described by Bruehl.

The second pillar of the study is the investigation prospectively of the efficacy of ascorbic acid in the prevention of CRPS following distal radial fracture in adults by means of a double blinded randomised control trial, utilising the validated criteria from pillar one for diagnosis of the condition.

CHAPTER TWO

HYPOTHESES AND STUDY QUESTIONS

2 HYPOTHESES AND STUDY QUESTIONS

2.1 HYPOTHESES

2.1.1 PILLAR ONE

The Atkins criteria for the diagnosis of complex regional pain syndrome (type 1) will identify a similar group of patients with the condition following a distal radial fracture when compared to the modified IASP criteria according to Breuhl. Therefore confirming the validity of this method for the diagnosis of CRPS for future research purposes in an orthopaedic setting.

2.1.2 PILLAR TWO

Complex regional pain syndrome (type 1) following distal radial fracture is due in part to the presence of an increased concentration of free radicals at the site of injury in the affected limb during the fracture healing process. Administration of the antioxidant, ascorbic acid as an oral preparation for the duration of fracture healing will act as a preventative measure against the build up of free radicals and therefore prevent the occurrence of complex regional pain syndrome (type 1) when compared to a placebo.

A statistically significant decrease in the incidence of complex regional pain syndrome (type 1) following fracture by administration of an antioxidant compared to placebo supports strongly the role of toxic free radicals in the pathophysiology of the disease.

The use of ascorbic acid administered in the early stages of fracture healing can provide a simple, cost effective and safe preventative measure against the occurrence of complex regional pain syndrome (type 1) following injury.

2.2 PRIMARY STUDY QUESTIONS

2.2.1 PILLAR ONE

1. Does the diagnostic criteria for complex regional pain syndrome as described by Atkins agree with the up to date IASP diagnostic criteria described by Bruehl when used to assess a series of patients following a distal radial fracture?

2.2.2 PILLAR TWO

2. Does the administration of ascorbic acid 500mg once daily for fifty days following injury reduce the incidence or prevent the development of complex regional pain syndrome (type 1) following a closed distal radial fracture?

3. If the incidence of complex regional pain syndrome (type 1) is not significantly altered following administration of ascorbic acid, does the treatment:

a. Improve any of the individually measured features of the condition occurring in the affected hand (pain, tenderness, finger stiffness, grip strength, finger swelling)?

b. Reduce the occurrence of other features of the condition occurring in the affected hand (vasomotor instability, motor dysfunction and trophic changes)?

2.3 SECONDARY STUDY QUESTIONS

2.3.1 PILLAR ONE

The data collected allowed the following additional questions to be discussed:

1. Does history of current or recent smoking increase the risk of developing complex regional pain syndrome following a distal radial fracture?

2. Is there an association between the time immobilised in a cast and the occurrence of complex regional pain syndrome?

CHAPTER THREE

METHODOLOGY

PILLAR ONE

3 METHODOLOGY PILLAR ONE:

THE VALIDATION OF THE ATKINS' CRITERIA IN THE DIAGNOSIS OF COMPLEX REGIONAL PAIN SYNDROME (TYPE 1)

3.1 INTRODUCTION

A lack of simple diagnostic test has led to an assorted array of diagnostic standards employed in studies thus far (van de Beek et al. 2002). The International Association for the Study of Pain (IASP) introduced the term complex regional pain syndrome and a set of initial diagnostic criteria (Stanton-Hicks et al. 1995). Since then refinement has been sought in order to provide an accurate and usable diagnostic tool both in clinical and research practice.

The lack of uniformity of diagnostic criteria amongst researchers has led to doubt as to the validity and interpretation of several prospective studies that have reproducibly shown that CRPS is a common condition, affecting patients with limb trauma (Harden et al. 2003).

Prospective studies employing a reproducible set of diagnostic criteria, employing in part objective assessment tools, have demonstrated that the incidence of CRPS is between 19% and 37% following both distal radial fractures (Atkins et al. 1989a; Atkins et al. 1990; Bickerstaff et al. 1994; Livingstone et al. 2002) and tibial fractures (Sarangi et al. 1993). These studies have also demonstrated the link between plaster tightness (Field et al. 1994) and the onset of the condition and the

ineffectiveness of regional guanethidine blocks in the treatment of the condition in the acute phase (Livingstone et al. 2002). Other researchers, using different diagnostic criteria have also shown similar incidences following distal radial fractures (Zollinger et al. 1999) and total knee replacement surgery (Stanos et al. 2001). A criticism of these studies has been the lack of validation of the diagnostics methods employed.

In order to test the validity of the diagnostic criteria according to Atkins, a series of patients presenting with a distal radial fracture were analysed. The data collected was used to diagnose CRPS both with the Atkins' criteria and those of the modified IASP criteria (Bruehl's criteria). This diagnostic method provides a sensitive and specific clinical test for CRPS and has been internally and externally validated using patients with non-CRPS neuropathic pain (Bruehl et al. 1999) (Harden et al. 1999)

3.2 STUDY METHODOLOGY

A series of two hundred and sixty-two adult patients that had attended the Bristol Royal Infirmary with a closed unilateral distal radial (Colles') fracture was reinvestigated. These patients had been part of a group recruited for a previous study on the effect of guanethidine blockade in the early management of CRPS (Livingstone et al. 2002). The raw prospective data collected by the original author (Mr James Livingstone) was reanalysed. No new data was created other than that of the comparative analysis of the original study data.

All patients were aged eighteen years or older. The fractures were managed by manipulation under appropriate sedation or regional anaesthesia into a satisfactory position and immobilisation in a forearm plaster. Inclusion in the study did not

influence fracture management. Injuries that had required stabilisation with external fixators or open reduction and internal fixation were excluded. Also excluded were patients with any other ipsilateral or collateral upper limb injury, significant pre-existing upper limb pathology and those who were unable to cooperate fully with the assessments.

Local ethics committee approval was obtained prior to the start of the original study and all patients gave informed consent to study participation.

3.3 DIAGNOSTIC METHODOLOGY

A full clinical assessment to determine the presence of the salient features of CRPS (type 1) was performed at an average of 66.3 days following injury by a single clinician (Mr James Livingstone). The following responses and measurements were recorded:

- Pain was assessed by direct questioning and finger tenderness by dolorimetry.
- Vasomotor instability was assessed using a standardised questionnaire (Atkins et al. 1989a) and clinical examination.
- Direct questioning and clinical examination assessed motor, trophic, oedema and sudomotor changes.
- Finger stiffness was assessed using goniometry.

From this assessment, the presence or absence of CRPS (type 1) was determined using both the Bruehl and the Atkins criteria.

The Atkins' criteria uses finger dolorimetry, finger goniometry in addition to a vasomotor instability questionnaire. To fulfil the Atkins' criteria for CRPS patients must have a vasomotor score of three or more, abnormal finger tenderness and abnormal finger stiffness. The association of these three features in the diagnosis of CRPS has been previously assessed with log linear analysis (Livingstone 2000). Bruehl's modified IASP criteria divide the array of abnormal clinical signs and symptoms of CRPS into four groups: sensory, oedema and sudomotor, vasomotor and motor/trophic. In order to fulfil Bruehl's criteria patients must report abnormal pain, symptoms in all four groups and have signs present in at least two of the groups (table 3).

Table 3 modified IASP diagnostic criteria for CRPS

Continuing pain that is disproportionate to any inciting event.

1.Must report at least one *symptom* in each of the following categories:

- ***Sensory***: Reports of hyperaesthesia.
- ***Vasomotor***: Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry.
- ***Sudomotor/Oedema***: Reports of oedema and/or sweating changes and/or sweating asymmetry.
- ***Motor/trophic***: Reports of decreased range of movement and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin).

2.Must display at least one *sign* in two or more of the following categories:

- ***Sensory***: Evidence of hyperalgesia and/or allodynia.
- ***Vasomotor***: Evidence of temperature asymmetry and or skin colour changes and/or asymmetry.
- ***Sudomotor/Oedema***: Evidence of oedema and/or sweating changes and/or sweating asymmetry.
- ***Motor/Trophic***: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin).

3.4 NORMAL RANGES AND REPRODUCIBILITY STUDIES

The reference ranges for of finger dolorimetry and finger goniometry values were calculated using control subjects of similar age with no known fractures or upper limb pathology. The reference ranges were calculated as the mean ± 2 standard deviations. Reproducibility of these measurements was assessed by re-examining twelve of the control group on a separate occasion. Coefficients of variation were then calculated to express the degree of reproducibility.

3.4.1 Sensory abnormality

The presence of abnormal pain and allodynia (mechanical and thermal) in the hand and forearm was recorded after direct questioning. Finger tenderness in both hands was assessed using finger dolorimetry to provide a ratio of affected to unaffected hand. This method has been shown previously to be reproducible (Atkins et al. 1989b). The reference range for the expected dolorimetry ratio in normal subjects in this study was 1.15 to 0.85. The coefficient of variation was 6.3%.

3.4.2 Oedema and sudomotor abnormalities

Patients were questioned on changes in the appearance of their hand since their injury had occurred. Excessive sweating in the affected hand was also recorded. Assessment of hand swelling was made by clinical examination and by water

displacement using a graduated Perspex cylinder. Abnormal sweating noted on clinical examination was recorded.

3.4.3 Vasomotor abnormalities

Vasomotor changes since the injuries were assessed using a standardised questionnaire (Atkins et al. 1989a). A positive response to a question was scored as 1. For the Atkins criteria a score of three or more was deemed to be abnormal. Both hands were assessed clinically and any asymmetry of skin colour, temperature or sweating documented.

3.4.4 Motor and trophic changes

Patients were asked directly whether they had noticed any changes in fingernail growth or thickness or the presence of new or thicker hair growth affecting the hands. Recording the presence of grip strength changes, fine motor control problems or new onset tremor, assessed subjective motor dysfunction.

Both hands were examined and any asymmetry of skin, fingernails or hair recorded. Grip strength was measured using a Jamar dynamometer. Finger stiffness was assessed using a finger goniometer. The range of finger movements for each hand was assessed by measuring maximum flexion at all of the joints of all four fingers. The readings obtained were summed for each hand. The total of the affected hand was then subtracted from the total of the unaffected hand to give a finger stiffness value. The reference range for the expected finger stiffness value in normal

subjects in this study was + 61 degrees to – 61 degrees. The coefficient of variation was 16.8%.

3.5 STATISTICAL ANALYSIS AND DATA PROCESSING.

Data from this part of the study was stored on a personal computer (MacBook Pro, Apple inc.). The original data had been stored and processed on the following personal computer (K&K Pentium processor, K&K computers). Data analysis was performed using the following software.

Windows 95 (Microsoft Corporation, USA)

Microsoft Excel 6.0 (Microsoft Corporation, USA)

Microsoft Excel 2008 for Mac (Microsoft Corporation, USA)

SPSS for Windows (Versions 7.0, and 11.5)

CHAPTER FOUR

METHODOLOGY

PILLAR TWO

4 METHODOLOGY PILLAR TWO:

THE EFFICACY OF ASCORBIC ACID (VITAMIN C) IN THE PREVENTION OF COMPLEX REGIONAL PAIN SYNDROME (TYPE 1) FOLLOWING DISTAL RADIAL FRACTURE

4.1 STUDY DESIGN

4.1.1 Inclusion criteria for study

Patient recruitment was approved by and occurred in two centres, Bristol Royal Infirmary and Weston General Hospital.

All patients with closed, unilateral fractures of the distal radius over the age of fifty years who met the inclusion and exclusion criteria attending one of the hospitals involved in the trial were asked to take part in the study. Patients were recruited as soon after their injury as possible. A combination of direct referrals from the emergency department and by examination of case notes and plain radiographs of patients waiting for fracture clinic review were employed. All patients were asked to commence their allotted trial medications on the day of recruitment. Patients were seen at a minimum of four weeks following their plaster removal and assessed for the presence or absence of complex regional pain syndrome.

4.1.2 Consent and ethical committee approval

All patients who agreed to take part in the study were given a full verbal and written explanation of the study design and the nature of complex regional pain syndrome and its incidence following distal radial fracture (Appendix 1). Written consent was obtained from each patient prior to them joining the trial (Appendix 2). Their general practitioners were informed of their study inclusion (Appendix 3). Full local ethical committee and research department approval was obtained from each of the hospitals taking part prior to the study commencing.

United Bristol Healthcare Trust Ethics Committee Log No. E5611
United Bristol Healthcare Trust Research Department Log No. SU/2003/1359
Weston Area Health NHS Trust Research Department Log No. E375

4.1.3 Exclusion criteria:

1. Patients with other ipsilateral or contralateral upper limb injury
2. Patients with dementia who are unable to co-operate fully with the assessment.
3. Patients with pre-existing hand pathology that would effect the measurements when comparing the contra lateral limb (e.g. severe rheumatoid arthritis or Dupuytren's contracture).
4. Patients less than 50 years old.
5. Patients treated with orthopaedic implants or external fixators.
6. Patients currently taking a therapeutic dose of ascorbic acid for medicinal reasons.

7. Pregnancy.

4.1.4 Initial assessment

At the time of recruitment a trial proforma was completed (Appendix 4). Information recorded included personal details, date and time of the injury, type of initial treatment, history of smoking and current vitamin or multivitamin usage.

4.2 FRACTURE MANAGEMENT

The management of individual patients and their fractures was not influenced by the study. The primary injury assessment was performed by a member of the emergency department of either of the recruiting centres.

Initial fracture reduction, if required, was carried out in the emergency department as per the departmental guidelines. Patients were referred to the next available fracture clinic and remained under the care of the consultant in charge. Routine follow-up included review at one and two weeks with an anteroposterior and lateral radiograph in plaster to determine the position of the fracture.

Patients subsequently requiring remanipulation and stabilisation with percutaneous kirschner wires were not excluded. Remanipulation was not usually attempted after the second week. The attending orthopaedic surgeon determined the period of immobilisation. Physiotherapy was commenced following plaster removal at the discretion of the attending orthopaedic surgeon.

4.3 RANDOMISATION

The Bristol Royal Infirmary pharmacy department using a block randomisation method performed trial medication randomisation. Patients were allotted a trial number that was recorded on all documentation and capsule bottles.

4.4 TRIAL MEDICATIONS

Patients were randomised to one of two treatment arms, ascorbic acid or placebo. The course of treatment was for 50 days. Both groups received their medications enclosed in a gelatin capsule (DHP Ltd, Crickhowell, UK) produced by the Bristol Royal Infirmary Pharmacy Department. One group received five hundred milligrams of ascorbic acid (Alpharma Ltd, Barnstaple, UK) divided into two capsules to be taken once daily. The other a lactose tablet placebo (Penn Pharma Ltd, Tredegar, UK) divided into two capsules to be taken once daily. Patients were asked to commence their trial medications on the day of recruitment.

Patients were asked to return their pill bottles at the end of trial assessment; compliance was recorded by counting any remaining capsules.

4.5 OUTCOME FOLLOWING FRACTURE IMMOBILISATION AND TRIAL MEDICATIONS

The study end point was the presence or absence of complex regional pain syndrome (type 1) at a minimum of four weeks following plaster removal. Assessment was made using diagnostic criteria described by Atkins (Atkins et al. 1989a). The use of finger dolorimetry, finger movements and a questionnaire for vasomotor instability has proved sensitive, quantitative and reproducible tests for the presence and severity of individual features of complex regional pain syndrome (type 1) following distal radial fracture. The Atkins criteria was employed for this section of the study rather than that of Bruehl, primarily due to the fact that this had been chosen during the initial study design and planning. The decision to compare the two criteria in Pillar 1 was made after ethical approval for Pillar 2 had been granted, and a change to this part of the study was felt not be warranted given the previous work performed using the Atkins methodology.

Before starting the final assessment further questions were asked regarding any problems encountered during plaster immobilisation. The extent and duration of any physiotherapy was recorded.

The returned medication bottles were inspected and any remaining capsules counted and recorded.

Predefined questions were then asked to each patient regarding symptoms and signs the patient had experienced only in the hand or fingers and specifically not in the wrist.

A 100mm visual analogue score supplemented pain assessment and the short form of the McGill Pain Questionnaire read to the patient and recorded by the author.
The patients' hand was examined for dystrophic and vasomotor changes. Measurements in the following order were then taken from both hands; finger movements, index finger swelling, grip strength and dolorimetry.

4.6 PROCESSING OF DATA

Data recorded during the study was stored on a personal computer (MacBook Pro, Apple inc, USA). Personal information recorded on each patient was not stored electronically in accordance with the Data Protection Act 1998. Only the unique randomised trial number identified the patient's computerised data entry. Paper records recording personal information were kept in a secure filing cabinet at all times.

The analysis and processing of data was performed on the pre-mentioned computer using the following software programmes:

Word processing; Microsoft Word 2008 (Microsoft®, USA)

Spreadsheet; Microsoft Excel (Office 2008) (Microsoft®, USA)

Statistics; SPSS for Mac (version 19.0) (IBM, USA)

4.7 STATISTICAL ANALYSIS

Data analysis was performed on a personal computer along with reference to the following texts:

Discovering Statistics Using SPSS (3rd Edition) A Field. Sage Books 2009.

Statistics at Square One. T D V Swinscow and M J Campbell. BMJ Books 2002.

Statistics at Square Two. M J Campbell. BMJ Books 2001.

Statistical advice was also provided by Ms Alison Smith B.Sc M.Sc, Statistician, Musculoskeletal Research Unit, Avon Orthopaedic Centre and by Professor Roger Atkins MA DM FRCS.

Data was analysed using standard methods for both nominal and continuous variables. For nominal variables Pearson's Chi squared test and Fisher' exact test was used. For continuous variables, data set means were analysed for normality using the Kolmogrov-Smirnov test and then analysed using a Students t-test or Mann-Whitney test as appropriate.

Statistical significance was defined as a p value of < 0.05.

4.8 STUDY SIZE CALCULATION

The number of patients required to complete the study in order to achieve adequate statistical significance was calculated using a comparison of proportions formula.

An estimate of the proportions expected to be affected in the two treatment arms of the study was based on previous work on the incidence of CRPS occurring following distal radius fracture by Atkins and others (Atkins et al. 1989a; Atkins et al. 1990; Field et al. 1997; Zollinger et al. 1999; Livingstone et al. 2002) and the incidence reported on by Zollinger following prophylactic treatment with ascorbic acid (Zollinger et al. 1999).

The expected incidence of CRPS in the placebo group was set at 25% and the predicted incidence in the ascorbic acid group was set at 10%.

The value for α and β for this calculation was set at 0.05 and 0.1 respectively to reduce the risk of type I and II errors. The study would therefore be powered at 90% with 95% significance.

The number of patients (n) needed in each treatment was calculated from the following equation (Campbell et al. 1995) without a continuity correction.

$$n > \frac{((z_2\alpha\sqrt{(2p(1-p))} + (z_2\beta\sqrt{(pA(1-pA) + (pB(1-pB)))})^2}{(pA-pB)^2}$$

Where:-

$z_2\alpha = 1.96$ (2 sided $\alpha = 0.05$)

$z_2\beta = 1.28$ ($1-\beta = 0.9$)

pA = expected proportion in the placebo group

pB = predicted proportion in the ascorbic acid group

$$p = \frac{pA + pB}{2}$$

4.9 STUDY SIZE RESULTS

The sample size (n) required to detect a difference in the expected proportion (25%) versus the predicted proportion (10%) at a power of 90% and 95% significance equals one hundred and thirty-one patients in each group.

4.10 PAIN ASSESSMENT INCLUDING DOLORIMETRY

4.10.1 INTRODUCTION

An accurate, quantifiable and reproducible objective assessment of pain for research purposes has thus far eluded researchers and clinicians. Historically differences between neuropathic pain and inflammatory mediated pain were apparently clearly defined by symptoms alone. As our understanding of the pathophysiology of pain mechanisms has improved these distinctions have become less clear.

Pain assessment tools vary in their level of objectivity and applicability. Laser Evoked Potentials uses laser stimulators to produce radiant heat pulses to selectively excite the free nerve endings of Aδ and C nociceptive fibres producing a quantitative objective response. Quantitative Sensory Testing analyses perception in response to an external stimulus, this may be mechanical or thermal in nature, can be objectively measured and quantified but requires a subjective evaluation by the patient.

Pain questionnaires rely entirely on patient subjectivity. The commonly used one-dimensional subjective tools to measure pain intensity are the Visual Analogue Scale (VAS), the Numeric Rating Scale (NRS), the Verbal Descriptor Scale (VDS) and the Faces scale. Descriptive pain assessment is performed with questionnaires such as the McGill Pain questionnaire. These different methods all have advantages and disadvantages.

No specific validated pain questionnaire exists for complex regional pain syndrome. As well as simple spontaneous pain at rest the condition may patient may also experience mechanical and thermal allodynia, hyperalgesia, hyperpathia and exercise induced pain. These pain phenomena require evaluation by direct questioning.

In this study a combination of simple questions requiring a yes/no answer to establish the occurrence of these phenomena was used with the short form of the McGill Pain Questionnaire (Melzack 1987) including a Visual Analogue Scale. Quantitative Sensory Testing was performed to distinguish abnormal finger tenderness.

4.10.2 FINGER DOLORIMETRY

The instrument to assess finger tenderness is a dolorimeter. First used to quantify articular finger tenderness in patients with rheumatoid arthritis (McCarthy et al. 1965), Kozin et al then applied it to the diagnosis and investigation of reflex sympathetic dystrophy (Kozin et al. 1976a). The technique has subsequently being used to investigate algodystrophy complicating distal radial fractures and tibial fractures (Atkins et al. 1989b; Sarangi et al. 1993; Bickerstaff et al. 1994; Field et al. 1994; Livingstone et al. 2002).

The dolorimeter is a modified commercial engineering compression extension gauge used in the compression mode that enables the investigator to apply a steadily increasing pressure to an anatomical site until a pain threshold is reached.

It consists of a hollow tube containing a spring that is fixed at a closed end. The free end of the spring sits in a metal cup that attaches to a metal rod that protrudes from the cylinder. A slit in the side of the cylinder allows a pointer attached to the metal cup to move up and down a graduated linear scale. To the end of the metal rod is attached a small plastic button ($0.5cm^2$) covered with orthopaedic felt. The dolorimeter used had a full-scale deflection of 5kg force. One kg force is equivalent to 20 Newtons per cm^2 pressure (Figure 6).

At each site on the hand to be examined the felt covered plastic button was steadied on the subjects skin to prevent slipping and compression was applied at a rate of approximately 1.5 kgF per second. The subject was instructed to say, "stop" as soon as the force being applied became uncomfortable. This command was standardised in all patients being assessed.

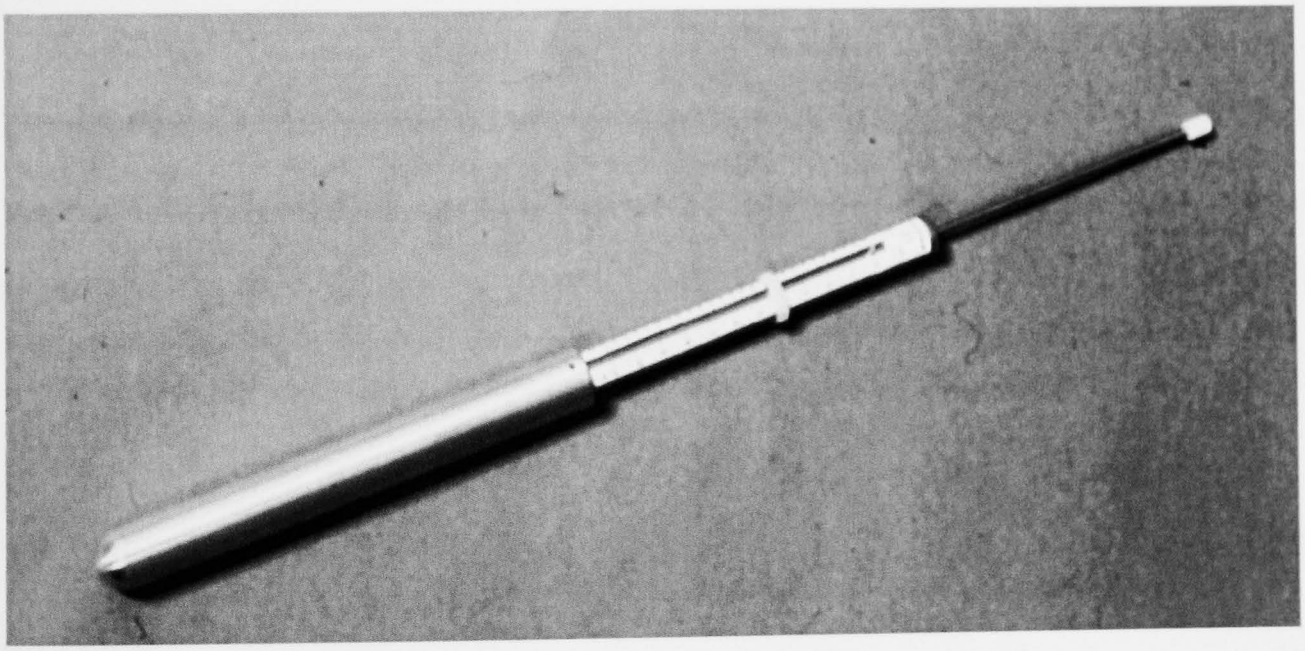


Figure 6 A dolorimeter

The assessment of hand tenderness was performed in a controlled fashion, to maximise reproducibility of the measurements taken. The subject's hands and forearms were placed flat on a table at a comfortable height. Sequential readings were taken from each finger in turn. Measurements were taken in turn from the dorsal surface overlying the metacarpophalangeal joint, the proximal phalanx, the proximal phalangeal joint, the middle phalanx and the distal interphalangeal joint. The thumb was not assessed.

The unaffected limb was assessed first followed by the affected limb. The measurements taken were summed and the total dolorimetry scores for each hand are expressed as a dolorimetry ratio by dividing the affected hand score by the unaffected hand score.

4.10.3 NORMAL RANGE

The investigators reference range was calculated by performing dolorimetry on the hands of nineteen healthy control subjects, selected at random from members of staff working in the Bristol Royal Infirmary Trauma and Orthopaedic clinic and patients without active or pre-existing pathology affecting their upper limbs.

The reference range was defined and calculated as the mean ± 2 standard deviations.

The standard error of the limit of the reference range was calculated as: $\sqrt{(3s^2/n)}$ where s=standard deviation and n=sample size.

The 95% confidence limits on these intervals were calculated accordingly: mean ± $2s \pm 1.96 \times \sqrt{(3s^2/n)}$.

4.10.4 TEST RELIABILITY

The reliability of the dolorimetry testing was performed on twelve control subjects and ten patients recruited into the trial who developed CRPS. The initial dolorimetry values were recorded and each subject re assessed within one hour. The reliability data sets were taken without cross-reference to the primary data sets.

In accordance with the recommendations of the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) group (Mokkink et al. 2010), the Intra-class correlation coefficients along with a standard error of measurement were calculated for the dolorimetry readings of individual sites on each finger, the whole finger, individual sites on all fingers, the whole hand and the dolorimetry ratios calculated.

The standard error of measurement was calculated accordingly:

$$\frac{\text{Standard deviation of the mean differences}}{\sqrt{2}}$$

4.10.5 RESULTS

The mean age of the group was 65 years (range 53 to 81 years). There were thirteen females and six males.

Individual dolorimetry values at were analysed between the two hands. A statistically significant difference was observed only at the ring finger proximal phalanx site (p=0.037) (Full results in Appendix 5a).

The mean dolorimetry ratio was 1.00 (standard deviation 0.092). A reference range of was thus calculated for this study of 1.18 to 0.82. (95% confidence intervals for this range were calculated as 1.13 to 1.23 and 0.77 to 0.87) (Full results in Appendix 5b).

Control group reliability

The intra-class correlation coefficient and standard error of the measurement for dolorimetry measurements of the whole right hand was 0.852 (95% CI 0.664-0.939) and 1234.99; for the left hand 0.572 (95% CI 0.184-0.805) and 1591.09 and for the dolorimetry ratio was 0.895 (95% CI 0.772-0.953) and 0.086 (Full results in Appendix 5c).

Complex Regional Pain Syndrome group reliability

The intra-class correlation coefficient and standard error of the measurement for dolorimetry measurements for the whole control hand was 0.996 (95% CI 0.984-0.999) and 1213.81, for the affected hand 0.997 (95% CI 0.988-0.999) and 833.20 and for the dolorimetry ratio was 0.992 (95% CI 0.970-0.998) and 0.073 (Full results in Appendix 5d).

4.11 FINGER STIFFNESS

4.11.1 INTRODUCTION

A number of methods have been described to quantifying finger stiffness. The simplest is a linear measurement from the fingertip to the distal palmar crease (Boyes 1955). The total active motion and total passive motion ranges (TAM, TPM) have been used to assess digital performance, especially after flexor tendon repair (Strickland 1985). The percentage loss of motion in a finger can be calculated through a complex combination of the measured finger joint motion using finger motion impairment tables described by Swanson et al. (1987). More recently computer aided motion analysis has been utilised to assess dynamic angular changes of each finger joint and the fingertip motion area for injured fingers. This method however requires specialist equipment and is time consuming to perform (Chiu et al. 2000). Active range of motion (AROM) assessment for finger stiffness using a goniometer remains a viable, quick and practical method both for clinical and research uses.

Subjective finger stiffness was documented prior to the objective assessment. Each patient was asked about the presence or absence of finger stiffness, whether this was a daily occurrence and whether it was throughout the day or only confined to the morning or evening.

An objective evaluation of finger stiffness was then made using a Perspex finger gonoimeter to measure the degree of maximal flexion at the joints of each finger in

both hands. A sum of these measurements gave a total reading for each hand. A finger stiffness value was calculated by subtracting the sum total for the affected hand from the sum total of the unaffected hand.

The goniometer readings were taken in a standardised fashion. The patients' hand was placed on a flat surface with the elbow flexed and the forearm and wrist in the neutral position.

The patient was asked first to make a fist to allow recording of maximum flexion at the metacarpal phalangeal joint and proximal interphalangeal joint of each finger. To allow measurement of maximum flexion at the distal interphalangeal joint, the patient was asked to extend the metacarpal joints and maintain full flexion at the proximal and distal interphalangeal joints.

4.11.2 NORMAL RANGE

The investigators reference range for the finger stiffness value was recorded using this method to evaluate the hands of nineteen healthy control subjects, selected at random from members of staff working in the Bristol Royal Infirmary Trauma and Orthopaedic clinic and patients without active or pre-existing pathology affecting their upper limbs.

The reference range was defined and calculated as the mean ± 2 standard deviations.

The standard error of the limit of the reference range was calculated as: $\sqrt{(3s^2/n)}$ where s=standard deviation and n=sample size.

The 95% confidence limits on these intervals were calculated accordingly: mean ± $2s \pm 1.96 \times \sqrt{(3s^2/n)}$.

4.11.3 TEST RELIABILITY

The reliability of this method of testing was performed on twelve control subjects and ten patients recruited into the trial who developed CRPS. The initial finger stiffness values were recorded and each subject re assessed within one hour. The reproducibility data sets were taken without cross-reference to the primary data sets.

In accordance with the recommendations of the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) group (Mokkink et al. 2010), the Intra-class correlation coefficients along with a standard error of measurement were calculated for the finger stiffness readings of individual sites on each finger, the whole finger, individual sites on all fingers and the whole hand.

The standard error of measurement was calculated accordingly:

$$\frac{\text{Standard deviation of the mean differences}}{\sqrt{2}}$$

4.11.4 RESULTS

The mean age of the group was 65 years (range 53 to 81 years). There were thirteen females and six males.

The mean cumulative finger flexion difference was 0 degrees (standard deviation = 31.13°). This gave a reference range for this study of -62.26° to 62.26°. (95% CI for this range = -79.40° to -45.12° and 45.12° to 79.40°). A statistically significant difference was observed only at the little finger metacarpal phalangeal joint site (p=0.002) (Full results in Appendix 6a & b).

Control group reliability

The intra-class correlation coefficient and standard error of the measurement for cumulative finger flexion of the right hand was 0.993 (95% CI 0.974-0.998) and 12.90, for the left hand 0.996 (95% CI 0.986-0.999) and 8.98 and for the cumulative finger flexion difference was 0.891 (95% CI 0.666-0.967) and 15.49 (Full results in Appendix 6c).

Complex Regional Pain Syndrome group reliability

The intra-class correlation coefficient and standard error of the measurement for cumulative finger flexion of the control hand was 0.999 (95% CI 0.996-1.000) and 3.92, for the affected hand 0.999 (95% CI 0.996-1.000) and 5.18 and for the

cumulative finger flexion difference was 0.996 (95% CI 0.983-0.999) and 6.81 (Full results in Appendix 6d).

4.12 VASOMOTOR INSTABILITY

4.12.1 INTRODUCTION

Vasomotor instability as an indicator of sympathetic nervous system dysfunction or an exaggerated inflammatory process is a key feature in the diagnosis of CRPS. The objective assessment of each component is time consuming, requires specialist equipment and testing must be performed in a carefully controlled environment. Previous clinical studies have utilized an eleven point screening questionnaire to determine recent features suggestive of vasomotor instability (Atkins et al. 1990). This tool focuses on the subjective presence or absence of temperature, colour, sweating and swelling changes noticed by the patient.

The same questionnaire was employed in this study, the questions were asked at the beginning of the assessment prior to any clinical examination of the subjects' hands to minimize bias.

The questionnaire has been previously validated and was also put to nineteen control subjects in this study. There were no positive answers recorded amongst this group.

The questions were:

1. Have you noticed any changes in the appearance of your hand compared to the other recently, and if so, what changes exactly?

2. Have you noticed any changes in the colour of your hand recently, and if so what?

3. Has your hand felt any different from the other hand recently, since the accident, and if so, in what way?

4. Has the temperature of your hand felt in any way different from the other hand recently, and if so in what way?

5. Has your hand been bluer than the other hand recently, or bluer than it was before the accident and if so under what circumstances?

6. Has your hand been redder than the other hand recently, or redder than it was before the accident and if so under what circumstances?

7. Has your hand felt warmer than the other hand recently, or warmer than it did before the accident and if so under what circumstances?

8. Has your hand felt cooler than the other hand recently, or cooler than it did before the accident and if so under what circumstances?

9. Has your hand responded differently to changes in environmental temperature recently, and if so in what way?

10. Have you noticed you hand going red and warm in a hot environment or blue and cold in a cool environment?

11. Does your hand sweat or perspire more than it used to or more than the other side recently?

4.12.2 CLINICAL EXAMINATION

Following this questioning, both hands were compared and assessed for any signs of vasomotor instability by the investigator. Specific features assessed and recorded were the presence or absence of colour changes, temperature difference, finger or hand swelling and sweating.

During this assessment specific trophic changes were also recorded; the presence or absence of fingernail changes (length, thickness and ridging), ectopic hair growth, skin changes and Dupuytrens nodules.

4.13 INDEX FINGER SWELLING

4.13.1 INTRODUCTION

Following clinical assessment of the subjects' affected hand and fingers for swelling, a quantitative evaluation was performed using an arthrocircometer to measure the circumference of the index finger. The device allows three simultaneous measurements to be taken by virtue of its structure. Three flexible metal strips, approximately 5 mm apart are attached to a plastic housing with a graduated scale along a recess for each metal strip. Each metal strip has a plastic marker to allow the reading of the measured circumference from the graduated scale. One end of the device is curved to allow the finger to sit comfortably against it during its use. The metal strips are tensioned against the skin of the finger and the circumference is recorded. To standardise the process the measurements are taken with the central metal strip centred over the proximal interphalangeal joint of the index finger.

Three readings are taken from the index fingers of both hands. The nine values are summed and an index finger ratio calculated by dividing the affected finger total by the unaffected finger total.

4.13.2 NORMAL RANGE

The investigators reference range for index finger swelling was calculated by assessing the index fingers of nineteen healthy control subjects, selected at random from members of staff working in the Bristol Royal Infirmary Trauma and

Orthopaedic clinic and patients without active or pre-existing pathology affecting their upper limbs.

The reference range was defined and calculated as the mean ± 2 standard deviations.

The standard error of the limit of the reference range was calculated as: $\sqrt{(3s^2/n)}$ where s=standard deviation and n=sample size.

The 95% confidence limits on these intervals were calculated accordingly: mean ± $2s \pm 1.96 \times \sqrt{(3s^2/n)}$.

4.13.3 TEST RELIABILITY

The reliability of the index finger swelling testing was performed on twelve control subjects and ten patients recruited into the trial who developed CRPS. The initial index finger values were recorded and each subject re assessed within one hour. The reliability data sets were taken without cross-reference to the primary data sets.

In accordance with the recommendations of the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) group (Mokkink et al. 2010), the Intra-class correlation coefficients along with a standard error of measurement were calculated for the index finger swelling readings from each hand.

The standard error of measurement was calculated accordingly:

$$\frac{\text{Standard deviation of the mean differences}}{\sqrt{2}}$$

4.13.4 RESULTS

The mean age of the reference range group was 65 years (range 53 to 81 years). There were thirteen females and six males.

The mean index finger swelling ratio was 1.01 (standard deviation = 0.17). This gave a reference range for this study of 0.67 to 1.35. (95% CI for this range = 0.58 to 0.76 and 1.26 to 1.44) (Full results in Appendix 7a).

Control group reliability

The intra-class correlation coefficient and standard error of the measurement for right index finger was 0.991 (95% CI 0.977-0.996) and 0.49, for the left hand 0.996 (95% CI 0.989-0.998) and 0.34 and for the index finger swelling ratio was 0.803 (95% CI 0.507-0.919) and 0.06 (Full results in Appendix 7b).

Complex Regional Pain Syndrome group reliability

The intra-class correlation coefficient and standard error of the measurement for the control index finger was 0.980 (95% CI 0.921-0.995) and 0.38, for the affected index finger 0.982 (95% CI 0.929-0.995) and 0.41 and for the index finger swelling ratio was 0.964 (95% CI 0.864-0.991) and 0.05 (Full results in Appendix 7c).

4.14HAND GRIP STRENGTH

4.14.1 INTRODUCTION

Handgrip strength was assessed using a Jamar dynamometer. The assessment was performed with the subject sitting, shoulder adducted to the side, elbow flexed to 90 degrees with the forearm and wrist in the neutral position.

Three consecutive readings were recorded from each hand and the mean reading calculated.

The grip strength ratio was calculated by dividing the affected hand mean reading by the unaffected hand mean reading.

4.14.2 NORMAL RANGE

The investigators reference range for grip strength was recorded using this method to evaluate the hands of nineteen healthy control subjects, selected at random from members of staff working in the Bristol Royal Infirmary Trauma and Orthopaedic clinic and patients without active or pre-existing pathology affecting their upper limbs.

The reference range was defined and calculated as the mean ± 2 standard deviations.

The standard error of the limit of the reference range was calculated as: $\sqrt{(3s^2/n)}$ where s=standard deviation and n=sample size.

The 95% confidence limits on these intervals were calculated accordingly: mean ± $2s \pm 1.96 \times \sqrt{(3s^2/n)}$.

4.14.3 TEST RELIABILITY

The reliability of this method of testing was performed on nineteen control subjects and twelve patients recruited into the trial. The grip strength values were recorded and each subject re assessed within one hour. The reliability data sets were taken without cross-reference to the primary data sets.

In accordance with the recommendations of the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) group (Mokkink et al. 2010), the Intra-class correlation coefficients along with a standard error of measurement were calculated for the grip strength readings of each hand.

The standard error of measurement was calculated accordingly:

$$\frac{\text{Standard deviation of the mean differences}}{\sqrt{2}}$$

4.14.4 RESULTS

The mean age of the group was 65 years (range 53 to 81 years). There were thirteen females and six males.

The mean grip strength ratio was 1.01 (standard deviation = 0.13). This gave a reference range for this study of 0.74 to 1.26. (95% CI for this range = 0.67 to 0.81 and 1.19 to 1.33) (Full results in Appendix 8a).

Control group reliability

The intra-class correlation coefficient and standard error of the measurement for grip strength measurements of the whole right hand was 0.988 (95% CI 0.969-0.995) and 1.14, for the left hand 0.995 (95% CI 0.988-0.998) and 0.71 and for the grip strength ratio was 0.792 (95% CI 0.537-0.914) and 0.09 (Full results in Appendix 8b).

Complex Regional Pain Syndrome group reliability

The intra-class correlation coefficient and standard error of the measurement for grip strength measurements for the whole control hand was 0.998 (95% CI 0.991-0.999) and 0.55, for the affected hand 0.996 (95% CI 0.991-0.999) and 0.91 and for the grip strength ratio was 0.925 (95% CI 0.728-0.981) and 0.03 (Full results in Appendix 8c).

CHAPTER FIVE

RESULTS

PILLAR ONE

5 RESULTS PILLAR ONE:

THE VALIDATION OF THE ATKINS' CRITERIA FOR THE DIAGNOSIS OF COMPLEX REGIONAL PAIN SYNDROME (TYPE 1)

5.1 INCIDENCE OF CRPS AND DIAGNOSTIC AGREEMENT

The incidence of CRPS (type 1) at nine weeks following injury was similar using either criteria (table 7). Fifty-four patients (20.61%) were diagnosed with CRPS (type 1) according to the Bruehl criteria and fifty-nine patients (22.52%) were diagnosed with CRPS (type 1) using the Atkins criteria. Using the Bruehl criteria as a gold standard, there was strong diagnostic agreement (kappa = 0.79, sensitivity = 0.87, specificity = 0.94).

Table 7 Incidence of Complex Regional Pain Syndrome according to criteria method

	CRPS	No CRPS	Total
Bruehl Criteria	54 (20.61%)	208 (79.39%)	262
Atkins Criteria	59 (22.52%)	203 (77.48%)	262

5.2 DIAGNOSTIC DIFFERENCES

Disagreement between the Breuhl and Atkins methods was found in nineteen out of two hundred and sixty-two patients (Table 8). The main difference between the two methods was found to be in pain assessment. Sixteen patients had abnormal pain, vasomotor instability, swelling, motor changes, an abnormal joint stiffness value and a vasomotor questionnaire score of three or more. Twelve of these patients did not complain of any sensory abnormalities (i.e. mechanical or thermal hypersensitivity). Their finger dolorimetry ratio however was lowered. Therefore these cases have CRPS (type 1) by the Atkins' criteria but not by Bruehl's method.

In contrast the remaining four patients in this sub-group had a normal finger dolorimetry ratio but abnormal forearm hypersensitivity and therefore had CRPS by Bruehl's criteria but not using the Atkins' method.

A further three patients differed due to their finger stiffness assessment. These all had CRPS using Bruehl's criteria but did not meet Atkins' criteria because despite having an abnormal vasomotor score and an abnormal finger dolorimetry ratio, their finger stiffness values were normal.

No other diagnostic differences were found in the remaining two hundred and forty-three patients.

Table 8 Diagnostic criteria differences

	Bruehl YES	Bruehl NO	Totals
Atkins YES	47	12	59
Atkins NO	7	196	203
Totals	54	208	262

5.3 DISCUSSION

Complex regional pain syndrome is commonly seen by two different sets of clinicians, orthopaedic surgeons and pain physicians. These two groups will see a somewhat different spectrum of disease and their clinical emphasis will be different. Thus the orthopaedic surgeon is likely to see patients at an earlier stage of disease evolution, the condition may be milder and there may be a greater propensity for self-resolution. The mainstay of treatment for these cases is likely to be physical therapy and analgesic medication and the orthopaedic surgeon's major concern will be restoration of normal joint movement. Such cases have previously been labelled "community CRPS" (Wilson et al. 2005). In contrast the pain physician will tend to see more severe refractory cases, which require more complex pain management and there will be a greater emphasis on pain relief.

These differences in clinical emphasis have led to researchers from the two specialities producing different criteria for the diagnosis of the condition, which has contributed to a lack of transparency of research between the disciplines.

The incidence of CRPS following distal radial fractures historically in retrospective studies is low (<2%) (Bacorn et al. 1953; Green et al. 1956; Frykman 1967; Plewes 1956; Cooney et al. 1980), however prospective studies of patients with injuries to the distal radius, tibia and following knee replacement in the acute, early stage of recovery from these conditions have repeatedly demonstrated a much higher incidence (11-37%) (Atkins et al. 1990; Schürmann et al. 2007). Some of these patients may be considered as having a sub clinical form of CRPS as they could be easily missed by the nature of the relative mildness of their symptoms and signs, however with detailed clinical assessment and the use of these diagnostic tools they

will be recognised in this form of prospective study. Fortunately most of these milder forms of CRPS will settle within twelve months of their onset, with reassurance, physical therapy and specific specialist pain management only when clinically indicated.

This study demonstrates that the Atkins and the modified IASP (Bruehl's) criteria for the diagnosis of CRPS are basically concordant, at least when applied to a group of patients with a homogeneous upper limb injury. The differences observed are caused by the emphasis on quantification of pain with a consequent concentration on the fingers to the exclusion of the remainder of the forearm.

By using finger dolorimetry to assess hypersensitivity, an area out of the zone of direct injury is objectively assessed, a distinction that is not a requirement of Bruehl's criteria.

Quantifying hypersensitivity using finger dolorimetry recognises that mechanical allodynia maybe sub clinically apparent to the patient and therefore exclude the diagnosis in some patients with CRPS using hypersensitivity as a subjective diagnostic requirement.

Another possible explanation for these sensory differences is that these patients are beginning to demonstrate impairment of sensory processing causing hypoaesthesia, a phenomenon that has been described in chronic cases of CRPS (Veldman et al. 1993).

There are some limitations to this study that warrant discussion. Firstly quantitative equipment to measure temperature or colour changes in the hands of our study population was not employed, these techniques have been well described

in other studies and would have increased the diagnostic accuracy and strength of these conclusions. However previous work by Perez suggests that clinician's assessment does correlate well with most measured values in CRPS patients (Perez et al. 2005).

The modified ISAP method of diagnosis has evolved from the original IASP criteria using patients with chronic symptoms and signs of CRPS referred to specialist pain units. These patients were assessed at an average of just over nine weeks following their injury in a relatively acute situation. It could therefore be argued that patients diagnosed with CRPS at this early stage are a completely different entity to the typical refractory patient seen in the pain clinic. This again raises the possibility that two different types of CRPS exist, one that resolves spontaneously and a more refractory type seen in the pain clinic. What is still unclear is whether these two extremes of the disease share the same pathophysiological mechanisms.

One may also question the clinical usefulness of these diagnostic tests. This study further highlights that these methods are really only best utilised as research tools. They are time consuming to perform in the busy clinic situation and furthermore with regards to the Atkins criteria, require baseline comparative data for each assessor or clinician for the calculation of abnormal dolorimetry and finger stiffness values. A simple, quick, sensitive and specific clinical test for CRPS remains a problem.

This study attempts to further validate those previous prospective studies that demonstrate a seemingly high incidence of CRPS following a range of common injuries and surgical interventions. This study therefore adds further evidence to support this finding. Awareness of a higher than commonly reported incidence of

CRPS will perhaps encourage clinicians to assess further those patients in whom persisting pain or restriction of limb function goes undiagnosed.

Whilst it is widely accepted that the majority of these patients labelled with CRPS using these diagnostic methods will settle within 12 months, those small numbers of patients that will not resolve are impossible to distinguish in the early stages of the condition.

CHAPTER SIX

RESULTS

PILLAR TWO

6 RESULTS PILLAR TWO:

THE EFFICACY OF ASCORBIC ACID (VITAMIN C) IN THE PREVENTION OF COMPLEX REGIONAL PAIN SYNDROME (TYPE 1) FOLLOWING DISTAL RADIAL FRACTURE

6.1 INTERIM ANALYSIS OF RESULTS

The aim of recruiting a total of two hundred and sixty-two patients in order to achieve the predetermined level of power and significance was unfortunately not possible.

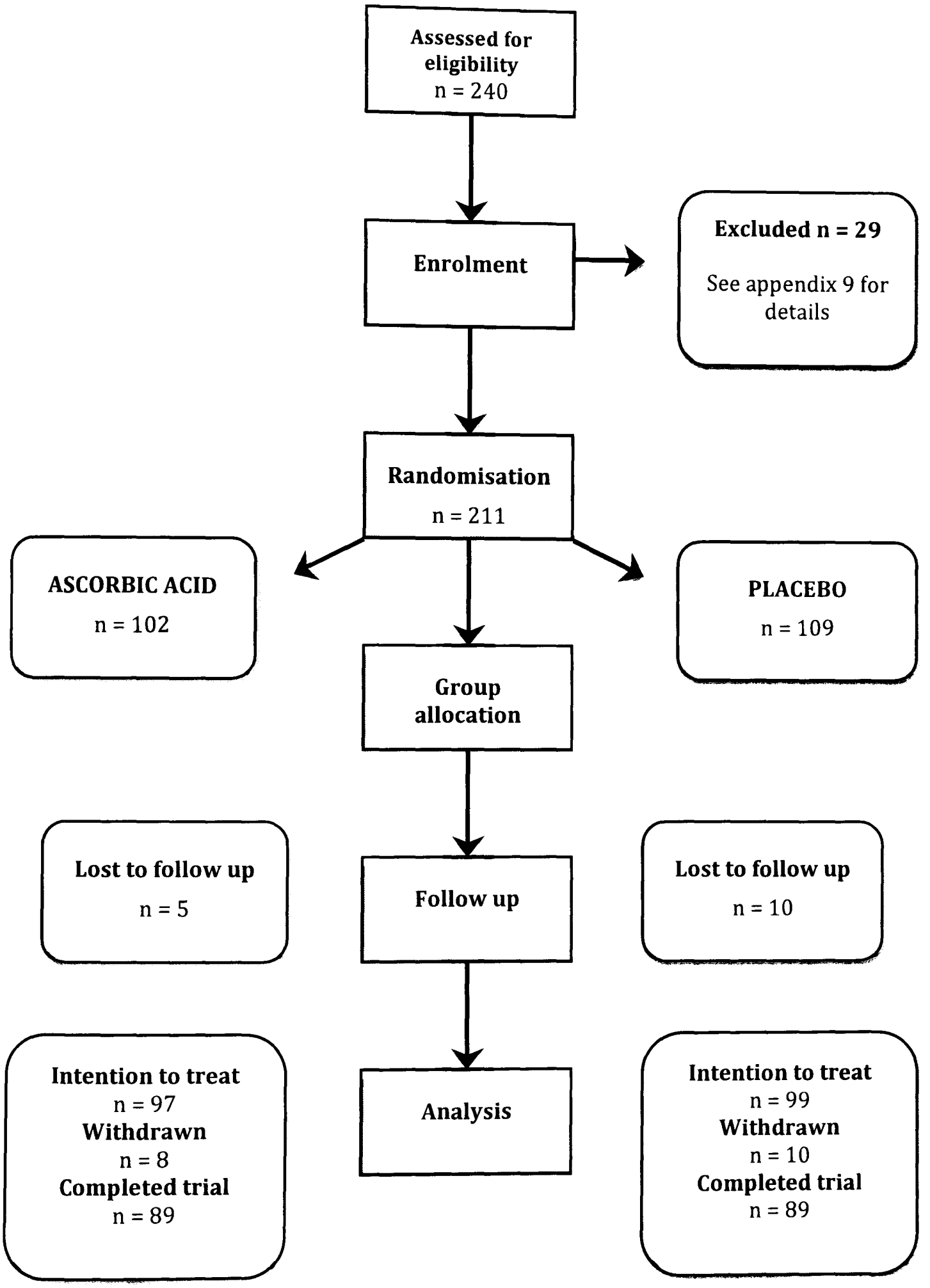
Due to an irresolvable problem with acquisition of placebo medication towards the end of the recruitment period the trial had to be halted early. Statistical advice was sort and a decision to perform an independent interim analysis of the results was made.

The results of the interim analysis revealed that attempts at further recruitment would be futile given both time restraints and the revised power study results.

6.2 STUDY EXCLUSIONS

A total of twenty-nine patients were assessed and excluded from participation in the study for various reasons (Figure 7) (Full details in Appendix 9).

Figure 7 Trial profile flow chart



6.3 STUDY WITHDRAWALS

Following study inclusion, randomisation and receipt of trial medication, a total of fifteen patients withdrew from the trial and were not assessed for the study end points.

Eight patients withdrew themselves from the trial and did not wish to take part in the study end point analysis. Five patients, despite multiple attempts, were unable to be contacted and therefore lost to follow up. One patient was withdrawn after developing significant dementia following a fall and subsequent proximal femoral fracture. A further patient developed significant symptoms from a cervical nerve root radiculopathy secondary to a previous cervical spine injury after inclusion that would have prevented a satisfactory clinical assessment (See Appendix 10 for full details).

6.4 PATIENT WITHDRAWALS PRIOR TO PER PROTOCOL ANALYSIS

Eighteen patients were assessed fully for the study end points but were withdrawn prior to the per protocol analysis, due to protocol breaches.

Sixteen patients returned bottles with trial medications remaining and therefore had not completed their study medications, one patient despite completing the study medications, volunteered she had taken a significant break during the study period due to ill health and one patient was excluded due to the requirement of

internal fixation of his wrist fracture following late displacement of the initial fracture reduction (See Appendix 11 for full details).

6.5 EFFECT OF ASCORBIC ACID ON THE INCIDENCE OF COMPLEX REGIONAL PAIN SYNDROME FOLLOWING A UNILATERAL CLOSED DISTAL RADIAL FRACTURE

6.5.1 METHOD OF ANALYSIS

The study results were analysed using both an intention to treat analysis and a per protocol analysis due to a number of withdrawals following study inclusion and randomization.

6.5.2 GROUP RANDOMIZATION AND COMPLIANCE

One hundred and two patients were randomised to receive ascorbic acid 500 milligrams, for fifty days and one hundred and nine patients were randomised to receive a lactose placebo.

The mean time following injury to study inclusion in the ascorbic acid group was 2.9 days (95% confidence interval 2.5-3.4 days, range 0-7 days). The mean time following injury to recruitment in the placebo group was 3.6 days (95% confidence interval 3.0-4.0 days, range 0-7 days). This difference was not significant (Mann Whitney U =3768.000, Z=-1.866, p=0.062).

Patients were asked to return their study medication bottles for assessment of compliance. In the ascorbic acid group seventy-one patients (73.2%) returned their study bottles empty, a further twenty-one (21.6%) stated the study capsules had been finished, but had disposed of their bottles prior to the CRPS assessment. Five patients (5%) returned bottles with capsules remaining. In the placebo group sixty-six (66.7%) returned empty bottles, twenty-five (25.3%) stated the study capsules had been finished but did not return their medication bottles and eight patients (8%) returned bottles with capsules remaining.

6.5.3 POST RANDOMISATION WITHDRAWALS AND INTENTION TO TREAT ANALYSIS

Thirteen patients (12%) from the ascorbic acid randomisation group were withdrawn following study inclusion, leaving eighty-nine patients in the per protocol analysis.

Twenty patients (18%) from the placebo randomisation group were withdrawn following study inclusion, leaving eighty-nine patients in the per protocol analysis.

End of study outcome assessments were performed on all patients, including those withdrawn due to the study protocol wherever possible. Ninety-seven patients were assessed for the presence or absence of complex regional pain syndrome in the ascorbic acid group. Ninety-nine patients were similarly assessed in the placebo group.

6.5.4 PATIENT REPORTED ADVERSE AFFECTS OR COMPLICATIONS

There were no patient reported adverse affects or complications that were attributable to the study medications

6.6 INCIDENCE OF COMPLEX REGIONAL PAIN SYNDROME

6.6.1 INTENTION TO TREAT ANALYSIS

There was no significant difference between the two groups in the incidence of complex regional pain syndrome diagnosed using the Atkins diagnostic criteria (chi-squared=1.196, p=0.305).

Sixteen patients (16.5%) in the ascorbic acid group and eleven patients (11.1%) in the placebo group were diagnosed with complex regional pain syndrome (Relative Risk=0.67, 95% confidence interval = 0.33-1.38) (table 9).

6.6.2 PROTOCOL TO TREAT ANALYSIS

There was no significant difference between the two groups in the incidence of complex regional pain syndrome after withdrawn subjects data had been excluded. (chi-squared=0.419, p=0.667).

Fourteen patients (15.7%) in the ascorbic acid group and eleven patients (12.4%) in the placebo group were diagnosed with complex regional pain syndrome (Relative Risk=0.79, 95% confidence interval=0.38-1.64) (table 9).

Table 9

Effect of Ascorbic acid on the incidence of complex regional pain syndrome

Intention to treat analysis

	Ascorbic acid	Placebo	Total	
CRPS	16	11	27	
No CRPS	81	88	169	
Unknown	5	10	15	
Total	102	109	211	**χ^2=1.196 p=0.305**

Per protocol analysis

	Ascorbic acid	Placebo	Total	
CRPS	14	11	25	
No CRPS	75	78	153	
Total	89	89	178	**χ^2=0.419 p=0.667**

6.7 EFFECT OF ASCORBIC ACID ON THE INCIDENCE AND SEVERITY OF THE FEATURES OF COMPLEX REGIONAL PAIN SYNDROME FOLLOWING A UNILATERAL CLOSED DISTAL RADIAL FRACTURE - INTENTION TO TREAT ANALYSIS

6.7.1 FINGER TENDERNESS ASSESSED BY DOLORIMETRY

Thirty-three patients (34%) in the ascorbic acid group and twenty-eight patients (28.9%) in the placebo group had abnormal finger tenderness, defined as a dolorimetry ratio of less than 0.82. There was no significant difference between the groups (chi-squared=0.598, p=0.536).

The mean dolorimetry ratio in the ascorbic acid group was 0.88 (95% confidence interval=0.84-0.92, range=0.38-1.30, median =0.91). The mean dolorimetry ratio in the placebo group was 0.88 (95% confidence interval=0.84-0.91, range=0.20-1.35, median=0.91). The dolorimetry ratios of the two groups were not significantly different (Mann-Whitney U =4739.500, Z=-0.34, p=0.973) (table 10).

There were significant associations across both groups between an abnormal dolorimetry ratio and any pain experienced in the hand or fingers (chi-squared=15.16, p=<0.0001), spontaneous hand or finger pain (chi-squared=4.969, p=0.037), exercise induced hand or finger pain (chi-squared=17.44, p=<0.0001) and allodynia of the hand or fingers (chi-squared=9.071, p=0.004) (table 11). There was a significant correlation between the visual analogue score and the

dolorimetry ratio (Pearson correlation coefficient=-0.387 (95% confidence interval -0.245 to -0.517), p=<0.0001) (Table 12).

6.7.2 PAIN ASSESSMENT

There was no significant difference between the ascorbic acid and placebo groups in the number of patients reporting any hand or finger pain (chi-squared=1.641, p=0.253); spontaneous hand or finger pain (chi-squared=0.324, p=0.631); exercise induced pain (chi-squared=2.463, p=0.148) and allodynia of the hand or fingers (chi-squared=0.370, p=0.594) (table 13).

The mean Visual Analogue Score (max score=100) in the ascorbic acid group was 23.0 (95% confidence interval 18.0-28.3, range 0-98, median=11). The mean score in the placebo group was 18.3 (95% confidence interval 14.0-23.1, range 0-88, median=0). There was no significant difference observed between the two groups (Mann Whitney U =4327.500, Z=-1.285, p=0.199).

The Short form McGill pain questionnaire (max score=39) total mean for the ascorbic acid group was 4.4 (95% confidence interval 3.3-5.7, range 0-27, median=1.5). The total mean score for the placebo group was 3.6 (95% confidence interval, range 0-27, median=0). The two groups total scores were not significantly different (Mann-Whitney U =4616.500, Z=-1.187, p=0.236) (table 10).

6.7.3 VASOMOTOR INSTABILITY

An abnormal vasomotor questionnaire score (max=11) of three or more was recorded in thirty-five patients (36.1%) in the ascorbic acid group and in thirty-eight patients (38.4%) in the placebo. There was no significant difference between the two groups (chi-squared=0.111, p=0.769). The mean vasomotor instability score in the ascorbic acid group was 2.4 (95% confidence interval 1.9-2.9, range 0-10, median=2). The mean vasomotor instability score in the placebo group was 2.2 (95% confidence interval 1.7-2.7, range 0-10, median=1). There was no significant difference between the two groups (Mann Whitney U = 4616.500, Z=-0.477, p=0.634).

Analysis of the occurrence of the features of vasomotor instability assessed by the vasomotor instability questionnaire demonstrated no significant difference between the two groups with respect to hand or finger swelling (chi-squared=0.013, p=1.000), colour changes in the hand or fingers (chi-squared=1.116, p=0.333), temperature difference between the hands (chi-squared=0.493, p=0.565) and excessive sweating (chi-squared=1.917, p=0.189) (table 13).

6.7.4 INDEX FINGER SWELLING

There was no significant difference observed following the analysis of finger swelling (p=<0.0001). Sixteen patients (16.5%) in each group had abnormal index finger swelling by virtue of an arthrocircometry ratio of 1.33 or greater.

The mean index finger arthrocircometry ratio observed in the ascorbic acid group was 1.09 (95% confidence interval 1.05-1.15, range 0.65-1.88, median=1.05). The mean index finger arthrocircometry ratio observed in the placebo group was 1.11 (95% confidence interval 1.06-1.15, range 0.71-1.69, median=1.09). No significant difference was observed between the two groups (Mann-Whitney U =4431.000, Z=-0.700, p=0.485) (table 10).

There was a significant association between the presence of reported hand or finger swelling in the vasomotor questionnaire and an abnormal index finger arthrocircometry ratio across the two groups (chi-squared=12.265, p=0.001) (table 15).

6.7.5 FINGER JOINT STIFFNESS

An abnormal range of flexion in the finger joints of the affected hand was defined as cumulative difference between the hands of -62 degrees or less. This was observed in thirty-five patients (36.1%) in the ascorbic acid group and thirty-five patients (35.7%) in the placebo group. No significant difference was detected (chi-squared=0.003, p=1.000).

The mean difference in cumulative finger joint range of motion in the ascorbic acid group was -59.5 degrees (95% confidence interval -78.3 to -43.4 degrees, range= -372 to +88 degrees). The mean difference in cumulative finger joint range of motion in the placebo group was -60.9 degrees (95% confidence interval -78.5 to -44.7 degrees, range= -400 to +56 degrees). There was no significant difference detected between the groups (Mann-Whitney U =4692.000, Z=-0.155, p=0.878) (table 10).

A significant association was observed between the presence of reported subjective finger stiffness and abnormal measured finger stiffness across the two groups (chi-squared=26.106, p=<0.0001) (table 16).

A significant association was also observed across both groups between the presence of abnormal measured finger stiffness and an abnormal index finger arthrocircometry ratio (chi-squared=26.002, p=<0.0001) (table 17).

6.7.6 GRIP STRENGTH

Seventy-five patients (78.9%) in the ascorbic acid group and seventy-nine patients (82.3%) in the placebo group had abnormal grip strength by virtue of a grip strength ratio of less than 0.73. No significant difference between the two groups was observed (chi-squared=0.342, p=0.587).

The mean grip strength ratio in the ascorbic acid group was 0.55 (95% confidence interval 0.51-0.60, range 0.10-1.17). In the placebo group the mean grip strength ratio was 0.54 (95% confidence interval 0.49-0.58, range 0.13-1.07). No significant difference was observed between the two groups (t-test, t=0.617, p=0.538) (table 10).

A significant association was demonstrated between patients reporting either a severe or slight grip weakness and an abnormal grip strength ratio across both groups (chi-squared=87.401, p=<0.0001, fishers exact test: p=<0.0001) (table 18).

6.7.7 TROPHIC CHANGES

Twenty-five patients (26.0%) in the ascorbic acid group and thirty-nine patients (39.4%) in the placebo group reported changes in fingernail growth in the affected hand. The difference noted was significant (chi-squared=3.941, p=0.049).

Eighteen patients (18.8%) in the ascorbic acid group and sixteen patients (16.2%) in the placebo group reported changes in hair growth in the affected hand or forearm. The difference was not significant (chi-squared=0.227, p=0.707) (table 10).

Significant associations across the two groups were observed between reported fingernail changes and observed fingernail changes (chi-squared=19.139, p=0.0001, fishers exact test: p=<0.0001) and reported hair growth changes and observed hair growth changes (chi-squared=59.691, p=<0.0001) (table 19).

6.7.8 MOTOR DYSFUNCTION

Patient reported fine motor control disturbances in the affected hand were recorded in thirty-six patients (37.5%) in the ascorbic acid group and forty-one patients (41.4%) in the placebo group. No significant difference was observed (chi-squared=0.312, p=0.661).

Eighteen patients (18.8%) in the ascorbic acid group and thirteen patients (13.1%) in the placebo group reported the presence of a tremor in the affected hand. No significant was observed (chi-squared=1.151, p=0.33) (table 10).

Table 10

Effect of ascorbic acid on the features of complex regional pain syndrome

Intention to treat analysis

	Ascorbic acid n=102	**Placebo** n=109	**Significance**
Visual Analogue Scale Mean (95% CI) Range (max score = 100)	n=97 23.0 (18.0-28.3) 0-98	n=99 18.3 (14.0-23.1) 0-88	U=4327.500 Z=-1.285 p=0.199
Short form McGill pain score Mean (95% CI) Range (max score = 39)	n=96 4.4 (3.2-5.7) 0-27	n=99 3.6 (2.5-4.8) 0-27	U=4321.500 Z=-1.187 p=0.236
Vasomotor Instability Score Mean (95% CI) Range (max score = 11)	n=97 2.4 (1.9-2.9) 0-10	n=99 2.2 (1.7-2.7) 0-10	U=4616.500 Z=-0.477 p=0.634
Dolorimetry ratio Mean (95% CI) Range	n=97 0.88 (0.84-0.92) 0.38-1.30	n=98 0.88(0.84-0.91) 0.20-1.35	U=4739.500 Z=-0.340 p=0.973
Abnormal dolorimetry ratio Yes No	n=97 33(34.0%) 64(66.0%)	n=98 28(28.6%) (71.4%)	χ^2=0.673 p=0.443
Index finger circumference ratio Mean (95% CI) Range	n=97 1.09 (1.05-1.15) 0.65-1.88	n=97 1.11 (1.06-1.15) 0.71-1.69	U=4431.000 Z=-0.700 p=0.485
Abnormal index finger circumference ratio Yes No	n=97 16 81	n=97 16 81	χ^2=<0.0001 p=1.000

Finger stiffness (degrees) (Cumulative ROM difference) Mean (95% CI) Range	n=97 -60 (-78 to -43) -372 to 88	n=98 -61 (-78 to -45) -400 to 56	U=4692.000 Z=-0.155 p=0.878
Abnormal finger stiffness Yes No	n=97 35(36.1%) 62(63.9%)	n=98 35(35.7%) 63(64.3%)	χ^2=0.003 p=1.000
Grip strength ratio Mean (95% CI) Range	n=97 0.55 (0.51-0.60) 0.10-1.17	n=96 0.54 (0.49-0.58) 0.13-1.07	t=0.617 p=0.538
Abnormal grip strength ratio Yes No	n=95 75(78.9%) 20(21.1%)	n=96 79(82.3%) 17(17.7%)	χ^2=0.342 p=0.587
Abnormal hair growth reported Yes No	n=96 18(18.8%) 78(81.2%)	n=99 16(16.2%) 83(83.8%)	χ^2=0.227 p=0.707
Abnormal finger nail growth reported Yes No	n=96 25(26.0%) 71(74.0%)	n=99 39(39.4%) 60(60.6%)	**χ^2=3.941** **p=0.049**
Fine motor control dysfunction reported Yes No	n=96 36(37.5%) 60(62.5%)	n=99 41(41.4%) 58(58.6%)	χ^2=0.312 p=0.661
Tremor reported Yes No	n=96 18(18.8%) 78(81.2%)	n=99 13(13.1%) 86(86.9%)	χ^2=1.151 p=0.330

Table 11

The relationship of reported pain and abnormal finger tenderness (dolorimetry ratio <0.83)

Intention to treat analysis

	Abnormal dolorimetry n=61	**Normal Dolorimetry** n=134	**Significance**
Any pain symptoms Yes No	 42(68.9%) 19(31.1%)	 52(38.8%) 82(61.2%)	**χ^2=15.157** **p=<0.0001**
Spontaneous pain Yes No	 23(37.7%) 38(62.3%)	 30(22.4%) 104(77.6%)	**χ^2=4.969** **p=0.037**
Pain on exercise only Yes No	 39(63.9%) 22(36.1%)	 43(32.1%) 91(67.9%)	**χ^2=17.444** **p=<0.0001**
Allodynia (mechanical or thermal) Yes No	 20(32.8%) 41(67.2%)	 19(14.2%) 115(85.8%)	**χ^2=9.071** **p=0.004**

Table 12

The relationship of reported pain (Visual analogue score) and finger tenderness (dolorimetry ratio).

Intention to treat analysis

	Pearson's correlation coefficient
Visual analogue score and Dolorimetry ratio	0.387 (95% CI 0.245-0.517) p=<0.0001

Table 13

Reported hand and finger symptoms following distal radial fracture

Intention to treat analysis

	Ascorbic acid n=97	**Placebo** n=99	**Significance**
Any reported pain			
Yes	51 (52.6%)	43 (43.4%)	χ^2=1.641
No	46 (47.4%)	56 (56.6%)	p=0.253
Spontaneous pain			
Yes	28 (28.9%)	25 (25.3%)	χ^2=0.324
No	69 (71.1%)	74 (74.7%)	p=0.631
Exercise induced pain			
Yes	46 (47.4%)	36 (36.4%)	χ^2=2.463
No	51 (52.6%)	63 (63.6%)	p=0.148
Allodynia			
Yes	21 (21.6%)	18 (18.2%)	χ^2=0.370
No	76 (78.4%)	81 (81.8%)	p=0.594

Table 14

Reported features of vasomotor instability

Intention to treat analysis

	Ascorbic acid n=97	**Placebo** n=99	**Significance**
Significant VMI score (>3)			
Yes	35(36.1%)	38(38.4%)	χ^2=0.111
No	62(63.9%)	61(60.6%)	p=0.769
Swelling			
Yes	38(39.2%)	38(38.4%)	χ^2=0.013
No	59(60.8%	61(60.6%)	p=1.000
Colour changes			
Yes	29(29.9%)	23(23.2%)	χ^2=1.116
No	68(70.1%)	76(76.8%)	p=0.333
Temperature difference			
Yes	45(46.4%)	41(41.4%)	χ^2=0.493
No	52(53.6%)	58(58.6%)	p=0.565
Excessive sweating			
Yes	10(10.3%)	5(5.1%)	χ^2=1.917
No	87(89.7%)	94(94.9%)	p=0.189

Table 15

The relationship of reported swelling and index finger circumference.

Intention to treat analysis

	Abnormal index finger arthrocircometry ratio n=32	**Normal index finger arthrocircometry ratio** n=162	**Significance**
Patient reported swelling			
Yes	21(65.6%)	53(32.7%)	**χ^2=12.265**
No	11(34.4%)	109(67.3%)	**p=0.001**

Table 16

The relationship of patient reported finger stiffness and measured finger stiffness.

Intention to treat analysis

	Abnormal finger stiffness n=69	**Normal finger stiffness** n=125	**Significance**
Patient reported finger stiffness			
Yes	49(71.0%)	41(32.8%)	**χ^2=26.002**
No	20(29.0%)	84(68.2%)	**p=<0.0001**

Table 17

The relationship of measured index finger circumference and measured finger stiffness

Intention to treat analysis

	Abnormal finger stiffness n=69	**Normal finger stiffness** n=125	**Significance**
Abnormal index finger arthrocircometry ratio			
Yes	24(34.8%)	8(6.4%)	**χ^2=26.002**
No	45(65.2%)	117(93.6%)	**p=<0.0001**

Table 18

The relationship between reported severe weakness and an abnormal grip strength ratio.

Intention to treat analysis

	Abnormal grip strength ratio n=153	**Normal grip strength ratio** n=37	**Significance**
Patient reported Severe weakness			**χ^2=87.401** **p=<0.0001** **Fisher's test** **p=<0.0001**
Yes	127(83.0%)	1(2.7%)	
No	26(17.0%)	36(97.2%)	

Table 19

The relationship between reported and observed trophic changes in the affected hand.

Intention to treat analysis

	Abnormal growth observed	**Normal growth observed**	**Significance**
Patient reported abnormal finger nail growth	n=14	n=181	**χ^2=19.139 p=<0.0001 Fisher's test p=<0.0001**
Yes	12(85.7%)	52(28.7%)	
No	2(14.3%)	129(71.3%)	
Patient reported abnormal hair growth	n=30	n=165	
Yes	20(66.7%)	14(8.5%)	**χ^2=59.691 p=<0.0001**
No	10(33.3%)	151(91.5%)	

6.8 COMPLEX REGIONAL PAIN SYNDROME RELATIONSHIPS.

The data of one hundred and ninety-six patients who were assessed for the presence or absence of CRPS were available for review as part of the intention to treat analysis to explore associations with the development of CRPS. Twenty-seven patients (incidence 13.8%) were diagnosed with CRPS and one hundred and sixty-nine patients were considered not be suffering with CRPS (table 20).

INTENTION TO TREAT ANALYSIS

6.8.1 CRPS AND GENDER

Of the twenty-seven patients with CRPS, twenty-five were female (92.6%). In the non-CRPS patient group one hundred and forty-seven patients were female (87.0%), this difference was not significant (Fishers exact test, p=0.540).

6.8.2 CRPS AND AGE

The mean age of the CRPS patient group was 67.4 years (95% confidence interval 64.0-70.7 years, range 51.0-83.1 years). The mean age of the non-CRPS patient group was 69.8 years (95% confidence interval 68.2-71.2 years, range 50.0-92.0 years). This difference was not significant (t=-1.174, p=0.242).

6.8.3 CRPS AND SMOKING

Six of the twenty-seven patients (22.2%) with CRPS regularly smoked tobacco. There were twenty-eight patients (16.6%) in the non-CRPS group who regularly smoked. This difference was not significant (chi-squared=0.519, p=0.583).

6.8.4 CRPS AND WORKING STATUS

Seventeen of the patients with CRPS were employed and ten were retired. There was no significant association observed between working status and the development of CRPS (chi-squared=1.100, p=0.359)

6.8.5 CRPS AND HAND DOMINANCE

There were no associations observed either with the side injured and the development of CRPS (chi-squared=2.422, p=0.143) or whether the side injured was dominant and the onset of CRPS (chi-squared=1.159, p=0.301).

6.8.6 CRPS AND REGULAR MULTIVITAMIN USAGE

Five patients (18.5%) within the CRPS patient group and sixteen patients (9.5%) in the non-CRPS group regularly took a multivitamin tablet prior to study inclusion. No significant association was observed between the regular intake of a multivitamin tablet prior to study inclusion and the development of CRPS. (Fishers exact test, p=0.178).

6.8.7 CRPS AND FRACTURE MANAGEMENT

One hundred and four patients (53.3%) required a manipulation as part of their fracture care. Twenty-one patients out of a total of twenty-seven who developed CRPS underwent a manipulation of their fracture, this association was significant (chi-squared=7.524, p=0.007).

Twenty patients required a remanipulation of their fracture. There was no significant association with the need for a remanipulation and the subsequent development of CRPS (chi-squared=<0.0001, p=1.000).

The mean time spent in cast in the CRPS patient group was 42.2 days (95% confidence interval 39.8-44.7, range 29-61 days). The mean time spent in cast in the non-CRPS patient group was 39.5 days (95% confidence interval 38.3-40.6, range 24-65).

A significant difference was observed in the time spent in cast in the CRPS group (median = 43 days) compared to the time spent in cast in the non CRPS group (median = 38 days) (Mann Whitney U= 1582.000, Z-score = -2.152, p =0.031).

Plaster problems were not significantly associated with the development of CRPS (chi-squared=4.057, p=0.053).

The need for physiotherapy prior to clinical study assessment and the development of CRPS was however significantly associated. (chi-squared=11.528, p=0.001) (Table 21).

Table 20

The relationship between the development of complex regional pain syndrome and patient demographic variables.

Intention to treat analysis

	CRPS (n=27)	**No CRPS** (n=169)	**Significance**
Gender			
Male	2(7.4%)	22(13.0%)	Fisher's test
Female	25(92.6%)	147(87.0%)	p=0.540
Age (Years)			
Mean (95% CI)	67.4 (64.0-70.7)	69.8 (68.2-71.2)	t=-1.174
Range	51.0-83.0	50.0-92.0	p=0.242
Smoking			
Yes	6(22.2%)	28(16.6%)	χ^2=0.519
No	21(77.8%)	141(83.4%)	p=0.583
Working status			
Working	10(37.0%)	46(27.2%)	χ^2=1.100
Not working	17(63.0%)	123(72.8%)	p=0.389
Side injured			
Left	12(44.4%)	102(60.4%)	χ^2=2.422
Right	15(55.6%)	67(39.6%)	p=0.143
Dominant arm Affected?			
Yes	14(51.9%)	69(40.8%)	χ^2=1.159
No	13(48.1%)	100(59.2%)	p=0.301

	CRPS (n=27)	**No CRPS** (n=169)	**Significance**
Multivitamins			
Yes	5(18.5%)	16(9.5%)	Fisher's test
No	22(81.5%)	153(90.5%)	p=0.178

Table 21

The relationship between the development of complex regional pain syndrome and fracture management variables.

Intention to treat analysis

	CRPS n=27	**No CRPS** n=169	**Significance**
Fracture manipulated			
Yes No	21(77.8%) 6(22.2%)	84(49.7%) 85(50.3%)	**χ^2=7.524** **p=0.007**
Fracture remanipulated			
Yes No	3(11.1%) 24(88.9%)	19(11.2%) 150(88.8%)	Fisher's test p=1.000
No. of days immobilized			
Mean (95% CI) Range	42.2 (39.8-44.7) 29-61	39.5 (38.3-40.6) 24-65	**U=1582.000** **Z=-2.152** **p=0.031**
Plaster problems reported			
Yes No	8(29.6%) 19(70.4%)	24(14.2%) 145(85.8%)	χ^2=4.057 p=0.053
Physiotherapy prior to assessment			
Yes No	17(63.0%) 10(27.0%)	50(29.6%) 119(70.4%)	**χ^2=11.528** **p=0.001**

6.9 STUDY GROUP DEMOGRAPHICS

The demographic data of the two treatment groups were analysed in order to demonstrate any significant differences within the variables collated. The data was subjected to both an intention to treat analysis and a per protocol analysis.

INTENTION TO TREAT ANALYSIS

6.9.1 AGE

The mean age of the ascorbic acid group was 69.7 (95% confidence interval 67.6-71.7, range 50.0-91.1). The mean age of the placebo group was 69.1 (95% confidence interval 67.1-70.9, range 51.0-92.0). No significant difference was observed (t-test, t=0.458, p=0.647) (table 22).

6.9.2 SEX

There were eleven males (10.8%) and ninety-one females (89.2%) in the ascorbic acid group. In the placebo group there were fourteen males (12.8%) and ninety-five females (87.2%). No significant difference was observed (chi-squared=0.214, p=0.696) (table 22).

6.9.3 SMOKING

Thirteen patients (12.7%) in the ascorbic acid group and twenty-five patients (22.9%) in the placebo group were regular tobacco smokers. This difference was not significant (chi-squared=3.706, p=0.072) (table 22).

6.9.4 EMPLOYMENT STATUS

Thirty patients (29.4%) in the ascorbic acid group and 31 patients (28.4%) in the placebo group were in regular employment. The remainder in each group were either retired or housewives. There was no significant difference in working status between the two groups. (chi-squared=0.024, p=0.881) (table 22).

6.9.5 INJURY SIDE AND DOMINANCE

Fifty-seven patients (55.9%) were left-handed and forty-five (44.1%) right handed in the ascorbic acid group. Sixty-five patients (59.6%) were left-handed and forty-four (40.4%) were right handed in the placebo group. There was no significant difference observed (chi-squared=0.304, p=0.676).

Forty-one patients (40.2%) in the ascorbic acid group and forty-nine (45%) patients in the placebo group had injured their dominant wrist. There was no significant difference observed (chi-squared=0.488, p=0.490) (table 22).

6.9.6 TREATMENT GROUPS STUDY PROTOCOL ANALYSIS

The mean time from day of injury to day of recruitment and commencement of study medications was 3.0 days (95% confidence interval 2.5-3.4, range 0-7) in the ascorbic acid group and 3.6 days (95% confidence interval 3.0-4.0, range 0-7) in the placebo group. There was no significant difference between the two groups (Mann-Whitney U=3768.000, Z=-1.866, p=0.062).

Patients were asked to return their study medication bottles as a marker of medication compliance and were also asked if they had managed to complete the fifty day treatment course. Ninety (92.8%) of the ascorbic acid group and ninety (90.9%) of the placebo group stated that they had taken their study medications as prescribed. No significant difference was observed (chi-squared=0.236, p=0.795).

Of the ascorbic acid group who had completed the study medications seventy-one (78.9%) returned their study medication bottles empty. Of the placebo group who had completed their study medications, sixty-six (73.3%) returned their study medication bottles empty. No significant difference was observed (chi-squared=0.764, p=0.485) (table 23).

6.9.7 FRACTURE MANAGEMENT

Fifty patients (49.5%) in the ascorbic acid group and sixty-three patients (57.8%) in the placebo group required a manipulation of their fracture as part of their initial fracture management. There was no significant difference observed (chi-squared=1.451, p=0.268).

Remanipulation of the fracture was required in twelve patients (11.8%) in the ascorbic acid group and in eleven patients (10.1%) in the placebo group. There was no significant difference observed (chi-squared=0.152, p=0.826).

The mean length of time spent in cast was 39.7 days (95% confidence interval 38.3-41.3, range 27-65) in the ascorbic acid group and 40.0 days (95% confidence interval 38.6-41.5, range 24-64) in the placebo group. No significant difference was observed (Mann-Whitney U =4035.000, Z=-0.669, p=0.505).

Physiotherapy was initiated in the fracture management following cast removal in thirty-six patients (35.3%) in the ascorbic acid group and thirty-one patients (28.4%) in the placebo group. No significant difference was observed (chi-squared=0.733, p=0.452) (table 24).

Table 22

Treatment groups demographic data

Intention to treat analysis

	Ascorbic Acid n=102	**Placebo** n=109	**Significance**
Age (years) Mean (95% CI) (Range)	n=102 69.7 (67.6–71.7) 50.0–91.1	n=109 69.1 (67.1–70.9) 51.0–92.0	t=0.458 p=0.647
Sex Male Female	n=102 11 (10.8%) 91 (89.2%)	n=109 14 (12.8%) 95 (87.2%)	χ^2=0.214 p=0.676
Smoker Yes No	n=102 13 (12.7%) 89 (87.3%)	n=109 25 (22.9%) 84 (77.1%)	χ^2=3.706 p=0.072
Employment Retired Employed Unemployed Housewife	n=102 69 (67.6%) 30 (29.4%) 1 (1%) 2 (2%	n=109 76 (69.7%) 31 (28.4%) 0 (0%) 2 (1.8%)	χ^2=0.024 p=0.881
Fractured wrist Dominant side? Yes No	n=102 41 (40.2%) 61(59.8%)	n=109 49 (45%) 60 (55%)	χ^2=0.488 p=0.490

Table 23

Trial medicine data

Intention to treat analysis

	Ascorbic Acid n=102	**Placebo** n=109	**Significance**
Days recruited post injury	n=92	n=92	U=3768.000 Z=-1.866
Mean (95% CI)	2.9 (2.5-3.4)	3.6 (3.0-4.0)	
Range	0-7	0-7	p=0.062
Trial medicines completed?	n=97	n=99	χ^2=0.236
Yes	90 (92.8%)	90 (90.9%)	p=0.795
No	7 (7.2%)	9 (9.1%)	
Trial medicine compliance	n=92	n=91	χ^2=0.764
Bottles empty	71 (77.2%)	66 (72.5%)	p=0.485
Bottles not returned	21 (22.8%)	25 (27.5%)	
Clinical assessment (Days post injury)	n=97	n=99	U=4586.000 Z=-0.452
Mean (95% CI)	83.4 (78.7-88.9)	82.1 (77.2-87.0)	
Range	55-192	54-156	p=0.589

Table 24

Treatment groups fracture management

Intention to treat analysis

	Ascorbic Acid n=102	**Placebo** n=109	**Significance**
Fracture manipulated	n=101	n=109	χ^2=1.451
Yes	50 (49.5%)	63 (57.8%)	p=0.268
No	51 (50.5%)	46 (42.2%)	
Type of anaesthesia used	n=50	n=63	Fishers test = 13.402
Biers block	26 (52%)	21 (33.3%)	
Haematoma block	9 (18%)	16 (25.4%	
Sedation	14 (28%)	25 (39.7%)	p=1.000
General anaesthetic	1 (2%)	1 (1.6%)	
Fracture remanipulated	n=102	n=109	χ^2=0.152
No	90 (88.2%)	98 (89.9%)	p=0.826
Yes	12 (11.8%)	11 (10.1%)	
Time in plaster cast (Days)	n=92	n=93	U=4035.000 Z=-0.669
Mean (95%CI)	39.7 (38.3-41.3)	40.0 (38.6-41.5)	
Range	27-65	24-64	p=0.505
Physiotherapy after cast removal	n=97	n=99	χ^2=0.733
Yes	36 (35.3%)	31 (28.4%)	p=0.452
No	61(59.8%)	68 (62.4%)	

6.10 PER PROTOCOL ANALYSIS

Other than no statistical significance detected in the incidence of reported fingernail changes between the two groups (p=0.054), there were no differences observed in the results for features of CRPS study group demographics or study protocol analysis when a per protocol analysis was applied to the study data.

These results are summarised in tabular form in Appendix 12.

6.11 DISCUSSION

The efficacy of ascorbic acid on the prevention or reduction in incidence of CRPS at a minimum of nine weeks following a distal radial fracture was investigated.
The evidence for a significant role for free radical induced tissue-damage, as an initiator in the pathogenesis of the condition is compelling. A small number of prospective and retrospective studies have demonstrated that administration of ascorbic acid may well prevent the development of CRPS in some individuals following a traumatic insult such as a fracture or elective surgery.

The results of this study demonstrate that the administration of ascorbic acid for a period of fifty days during fracture healing following a distal radial fracture did not influence the incidence of CRPS when diagnosed using a criteria that has been successfully validated against a widely accepted and reported on gold standard. In addition the individual features of CRPS in the hand such as pain, tenderness, finger stiffness, vasomotor instability and motor symptoms and signs which lead to much of the disability and suffering endured by individuals with the condition were not improved by administration of ascorbic acid. There was a statistically significant difference observed in the placebo group for reported incidence of fingernail growth using an intention to treat analysis ($p=0.049$).

The incidence of CRPS in the ascorbic acid group was in fact higher than in the placebo group, although with the numbers recruited, this was not statistically significant.

Based on an intention to treat analysis, to detect a difference of 5.4% (15.5% versus 10.1%) with a significance of 0.05 and a power of 0.80, a sample size of 601 per group (1,202 in total) would be required. For a power of 0.90, this would be 805 per group (1,610 in total), assuming no loss to follow up. Whether the observation of a potential deleterious affect of ascorbic acid on the occurrence of CRPS in this study is in deed true remains to be proven. This study is underpowered with respect to this observation; therefore these results and trends may simply reflect a type II error.

The incidence of CRPS in either group in this study is lower than those previous studies using the Atkins criteria (Atkins 1990; Bickerstaff 1994; Sarangi 1995; Livingstone 2002). The lower limit of the reference range for normal dolorimetry in this study was calculated as 0.82, which is lower than previous studies. Even allowing for this as a factor and reanalysing the results with the higher limit of 0.92 described by Bickerstaff et al, would only increase the yield of CRPS diagnoses to 20.59% in the ascorbic acid group and 16.51% in the placebo group.

Whilst this study cannot directly explain this finding, there may be a number of possible explanations. The care of distal radial fractures may have improved with regard to minimising the period of immobilisation and providing patients with lightweight, appropriately fitting upper limb casts that do not restrict finger and thumb movement, and do not increase the risk of cast induced swelling. There may be better patient education with regards to early and appropriate analgesia and anti-inflammatory medication, self-mobilisation and the importance of upper limb elevation to minimise swelling. The health of the population maybe changing for the better and the observed fall in incidence maybe an indirect marker of this.

Further studies are required to confirm this observation that may also allow the investigation of whether there are specific environmental or genetic factors involved.

The diagnostic criteria utilised differed from those of Zollinger's study. The elements of the Veldman criteria do not differ significantly from those of Atkins or Bruehl and it would therefore seem unlikely that the differences observed in this study could be attributable purely to the criteria used.

The length of prophylactic intervention, dosage and administrative route were all intentionally designed to mirror Zollinger's study to allow comparison.

This study was designed to allow recruitment of a continuous group of patients presenting with an acute injury. The ideal was to recruit patients on the day of injury but due to the nature of the fracture referral system to the orthopaedic fracture clinic and the large number of emergency department clinicians dealing with potential study participants this was not always possible. Although there was no statistical difference between the two treatment groups there was on average three days between injury and recruitment. It remains to be proven whether this factor had any bearing on the results observed in this study.

Although this study endured a not insignificant drop out rate, a problem not encountered in a previous similar study (Zollinger et al. 2007), there was no difference seen between the per protocol analysis and the intention to treat analysis with respect to the primary and secondary study questions.

Evidence from a variety of clinical and animal studies supports the benefits of antioxidant treatment in preventing symptoms and reducing the markers of free

radical damage or oxidative stress following acute injury, however other studies report conflicting results.

It is known that in vitro ascorbic acid acts as a pro-oxidant reacting with free iron to produce the ascorbate free radical, this is believed in healthy subjects not be of physiological significance, however in healthy subjects loaded with ascorbic acid and iron salts DNA damage in leukocytes has been observed (Rehman et al. 1998). Free iron release from tissue does however occur in the presence of inflammation (Biemond et al. 1984) and sepsis. Increasing levels of ascorbate free radical have been observed in septic patients supplemented with ascorbic acid compared to controls (Galley et al. 1996).

In a clinical study on healthy volunteers supplementation with either ascorbic acid and the water-soluble antioxidant N-acetyl cysteine or placebo following an exercise-induced acute muscle injury to the upper limb caused an increase in detectable antioxidant levels, free iron cellular damage markers and markers of oxidative stress in the treatment group. Subjective pain and arm range of movement were not significantly different at the study end point between the two groups (Childs et al. 2001).

Recently the benefits observed in an animal model of acute pancreatitis following antioxidant treatment have not been reproduced in a prospective blinded randomised human clinical trial. Supplementation with intravenous N-acetyl cysteine, selenium and ascorbic acid was compared to placebo, with a primary end point of organ dysfunction at seven days measured. Early interim analysis revealed no statistically significant difference between the two groups, for either the primary end point or other secondary end points. A trend towards increased mortality and organ dysfunction was noted in the treatment group (Siriwardena et al. 2007).

CHAPTER SEVEN

CONCLUSION

7 CONCLUSION

7.1 ANSWERS TO PRIMARY STUDY QUESTIONS

7.1.1 PILLAR ONE

1. Does the diagnostic criteria for complex regional pain syndrome as described by Atkins agree with the up to date IASP diagnostic criteria described by Bruehl when used to assess a series of patients following a distal radial fracture?

The results of the first pillar of this study comparing the Atkins criteria with those of the modified IASP criteria described by Bruehl when assessing a series of two hundred and sixty-two patients following a distal radial fracture for CRPS show a strong agreement between the two methods.

The incidence of CRPS at nine weeks following injury was 20.61% according to the Bruehl criteria and 22.52% using the Atkins criteria. Using the Bruehl criteria as a gold standard, there was strong diagnostic agreement (kappa = 0.79, sensitivity = 0.87, specificity = 0.94).

7.1.2 PILLAR TWO

2. **Does the administration of ascorbic acid 500mg once daily for fifty days following injury reduce the incidence or prevent the development of complex regional pain syndrome (type 1) following a closed distal radial fracture?**

In this study the incidence of CRPS following a distal radial fracture was not reduced or prevented when assessed for at a minimum of nine weeks following injury. There were a greater number of individuals diagnosed with CRPS in the ascorbic acid group (16.5%) than in the placebo group (11.1%), this was not statistically significant.

3. **If the incidence of complex regional pain syndrome (type 1) is not significantly altered following the administration of ascorbic acid, does the treatment:**
    - **Improve any of the individually measured features of the condition occurring in the affected hand (pain, tenderness, finger stiffness, grip strength, finger swelling)?**
    - **Reduce the occurrence of other features of the condition occurring in the affected hand (vasomotor instability, motor dysfunction and trophic changes)?**

In this study administration of ascorbic acid following a distal radial fracture did not significantly improve any of the individual disease features associated with

CRPS other than fingernail changes. The incidence of reported fingernail changes in the ascorbic acid group was 26.0% and in the placebo group 39.4% (p=0.049).

7.2 SECONDARY STUDY QUESTIONS

7.2.1 PILLAR ONE

1. Does history of current or recent smoking increase the risk of developing complex regional pain syndrome following a distal radial fracture?

In this study the incidence of a history of smoking was 22.2% in patients diagnosed with CRPS and 16.6% in patients diagnosed as non-CRPS. This difference was not statistically significant (p=0.583). This result would therefore support the view that the risk of developing CRPS is not increased by a history of smoking.

2. Is there an association between the time immobilised in cast and the occurrence of complex regional pain syndrome?

This study demonstrated that those individuals who developed CRPS were statistically more likely to have been immobilised in a forearm cast for longer than those assessed not to have developed CRPS. There was also a significant relationship between the need for fracture reduction and the development of CRPS, suggesting that those with a more significantly displaced fracture, requiring reduction and therefore perhaps a longer period of immobilisation may be at risk of developing CRPS. Length of time in cast maybe dictated by the clinical assessment

of fracture union, this includes assessment of tenderness over the fracture site. This feature maybe difficult to accurately assess in the patient who has developed CRPS and therefore additional cast time may be advised in these patients.

7.3 FUTURE RESEARCH

Many questions remain unanswered concerning CRPS, in particular what are the exact events that trigger the condition and does more than one condition exist under the umbrella of CRPS.

The role of the inflammatory system remains at the forefront of research into the pathophysiology of the condition and with the recent development of two interesting animal models to compliment ongoing human trials further knowledge and developments are anticipated.

This study is one of a small number that have investigated the potential of a simple, apparently safe and inexpensive intervention to prevent the development of CRPS following a traumatic insult. It is however the first to demonstrate that ascorbic acid may not prevent the onset of CRPS and in fact may increase the risk of developing it.

With compelling evidence in the literature suggesting a role for free radicals in the development of CRPS further studies are needed to investigate this theory. Further trials using validated diagnostic criteria are needed to confirm the results of this study that when given acutely after an injury ascorbic acid confers no benefit on the patient. As well as trials on patients following trauma, studies involving elective surgical interventions such as total knee replacements could be utilised. Such a population groups offers the advantage of a more controlled study group, which

allow some of the confounding factors encountered in a traumatic group, such as timing of administration of pharmaceutical interventions to be minimised.

Human trials may benefit from animal study confirmation of the role of antioxidants in the prevention or treatment of CRPS, such work would allow the investigation of different types and combinations of antioxidants and also whether timing of the intervention in relation to the insult has any bearing on the outcome.

The condition as a whole requires further assessment into its effect on functional outcome in a prospective setting. Whilst we know from historical studies that the majority of cases of post traumatic CRPS improve given time, the impact of the individual components of the condition, particularly pain, stiffness, motor dysfunction and sensory disturbance over time have not been fully assessed with contemporary functional outcome measures and quality of life scores. In addition to those patients who meet the criteria for a full-blown case of CRPS following trauma are those who have some features of the condition but not enough to meet the diagnostic criteria. It is plausible that these patients function are as affected as those labelled with CRPS, suggesting that the spectrum of CRPS needs to widened to include these patients to ensure that appropriate rehabilitation and pain management can be instigated.

CHAPTER EIGHT

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CHAPTER NINE

APPENDICES

9 APPENDICES

9.1 APPENDIX 1

Patient information sheet

University of BRISTOL

United Bristol Healthcare NHS

NHS Trust

Department of Orthopaedic & Trauma Surgery

PATIENT INFORMATION SHEET

A trial of the effectiveness of Vitamin C to prevent CRPS following wrist fracture

A double blind randomised controlled trial to compare Vitamin C 500mg daily and placebo in the prevention of Complex Regional Pain Syndrome (CRPS) in patients following wrist fracture

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends, family or your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
About one quarter of patients who fracture their wrist will develop a condition called Complex Regional Pain Syndrome (CRPS). CRPS causes pain, swelling and changes in the colour of the skin of the hand after a wrist fracture. The condition is usually temporary and most people's symptoms have settled after 1 year.
We would like you to help us test the effects of whether Vitamin C, taken as a tablet whilst your fracture is healing in a plaster, can stop CRPS occurring.

Why have I been chosen?
You have been invited to take part because you have fractured your wrist and have only required minimal treatment in a plaster cast so far. We cannot effectively test for CRPS in patients with certain hand or arm problems or who have had an operation on their fracture. You are therefore suitable to take part in this trial.

Do I have to take part?
No, taking part is voluntary. It is up to you to decide whether or not to take part. If you do decide to take part we will ask you to sign a consent form and give you a copy of this information sheet and the consent form to keep. If you decide to take part you are still free to withdraw at any time. If you decide not to take part you do not have to give a reason, nobody will be upset and the standard of care you receive will not be affected.

What will I be asked to do if I take part?
You will either be given the test drug (Vitamin C) or a placebo. A placebo is a dummy tablet that looks like the real thing but contains no active ingredients. You will be allocated to either Vitamin C or the placebo by chance, that is randomly, like flipping a coin. You have an equal chance of being allocated either Vitamin C or the placebo. The tablets are made to look identical so that neither you nor the research doctor will know which tablet you are taking. At the end of the trial we break the code to find out which tablet you a have been taking. We will ask you to take the tablet once a day for 50 days.
If you agree to join the study today we will ask you some questions about your general health and the how you fractured your wrist.
We will ask you to start the tablets from today.
Over the next few weeks you will be under the care of one of the orthopaedic consultants and will receive the normal standard care for wrist fractures that usually involves being in a plaster cast for up to six weeks.
When you return for your follow up appointment in the fracture clinic in nine weeks as well as the routine questions and examination that normally takes place at this appointment, you will be asked some specific questions about your hand and some simple measurements will be taken to assess the size of your hand and the movements in your fingers.
One of these measurements involves testing for any discomfort in your hand. The device we use for this is made from a piece of blunt plastic. It may cause you some discomfort for a few seconds. It does not involve a needle or any other sharp parts.
These tests and measurements will enable us to tell you whether you have CRPS or not. If you do develop CRPS we will refer you for treatment.

Will I need to attend any extra clinic appointments?
No. Instead of seeing one of the normal clinic doctors after you come out of plaster at nine weeks you will see the research doctor who will assess your hand for the presence of CRPS as well as ensuring your fracture as healed satisfactorily. This appointment will take about 30 minutes to complete.

What are my responsibilities?
During the study you will need to take the study tablets every day. It does not matter what time of day you take them. You may take all your usual tablets and any painkillers that you may need to take whilst your fracture is healing. When you come to the clinic in nine weeks please bring your study tablet bottle with you.

Can I buy and take my own Vitamin C tablets?

It is very important in this study that you do not buy and take Vitamin C tablets on top of the study tablets you have been given. If you do this will adversely affect the results of the study.

What other treatments are available?
At the moment there are no other known treatments to prevent CRPS occurring.

What are the possible side effects of taking part?
As far as we know taking Vitamin C 500mg once a day is entirely safe. It has been used in a wide range of trials for other medical conditions without any clinically significant side effects.

What are the possible benefits in taking part?
We hope that Vitamin C will help you more than the placebo, but this cannot be guaranteed. The information we get from this study may help us prevent or reduce the number of CRPS cases we see occurring after wrist fractures.

What if new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment being studied. If this happens your research doctor will discuss it with you and you can then decide whether you wish to continue in the study.

What happens when the research study is finished?
If you develop CRPS you will be referred for treatment. If you require treatment for any other condition related to you wrist fracture this will continue under the care of your orthopaedic consultant.

Will my taking part in this study be kept confidential?
Your medical records will only be examined by the research doctor. No outside body or drug company is involved with this trial.

Will my GP be informed of my involvement in this study?
Yes we will inform your GP so he/she understands the reason why you have been asked to take a tablet whilst your fractured wrist is healing. If you do not want your GP to know about your involvement in this trial this would prevent you from taking part. Again this will not affect your treatment and you do not have to tell us why you do not want your GP informed.

What will happen to the results at the end of the research study?
The results of this study will not be known until sometime after the last patient in the study has been examined (in about 18 months time). The research doctor will let you know the results and which treatment you were taking. The results will be reported in professional publications or meetings but you will not be identified by name.

Who has reviewed the study?
The United Bristol Healthcare Trust Research Ethics Committee and Weston Local Research Ethics Committee has approved the study.

Thank you for considering taking part in this research.

Mr Andrew McBride MRCS(Ed)
Clinical Research Fellow
Department of Orthopaedic & Trauma Surgery
Bristol Royal Infirmary
Tel: 0117 928 2878

Version No. 2 April 2003

9.2 APPENDIX 2

Consent form

University of BRISTOL
United Bristol Healthcare NHS
NHS Trust

Department of Orthopaedic & Trauma Surgery

CONSENT FORM

A trial of the effectiveness of Vitamin C to prevent CRPS following wrist fracture

Patient ID trial: ☐

Patient ID No. for ☐

Please initial box

I confirm that I have read and understand the information sheet dated_____ (version_____) for the above study and have had the opportunity to ask questions. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Mr Andrew McBride
Clinical Research fellow
Department of Orthopaedic & Trauma Surgery
Bristol Royal Infirmary
Marlborough Street
Bristol BS2 8HW
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March 2004 (Version 2)

9.3 APPENDIX 3

General practitioner information sheet

University of BRISTOL

United Bristol Healthcare NHS

NHS Trust

Department of Orthopaedic & Trauma Surgery

GENERAL PRACTITIONER INFORMATION SHEET FOR CLINICAL TRIAL

Prevention of Complex Regional Pain Syndrome after Wrist fractures

Your patient:

HAS AGREED TO TAKE PART IN THE FOLLOWING RCT:

Complex Regional Pain Syndrome (CRPS) is a little understood condition comprising of excessive tenderness, swelling, joint stiffness and colour, temperature and sweating abnormalities of the arm or leg that may occur following an injury.

For every four people who fracture their wrist one person will develop a form of CRPS. This is usually a mild form and symptoms settle over four to six months. The more severe form is less common but causes considerable disability and is often difficult to treat successfully.

CRPS maybe caused by free radical induced damage

Vitamin C may help to reduce the chances of developing CRPS following wrist fracture.

We would like to assess scientifically the effectiveness of Vitamin C in reducing or preventing patients getting CRPS after a wrist fracture and this can only be done

through a PROSPECTIVE, RANDOMISED, DOUBLE BLIND, CONTROLLED clinical trial.

We are asking all patients over 50 years old with a wrist fracture to take part in a study where some patients will be given Vitamin C tablets and some patients will be given a sham or placebo tablet which has no effect.

Involvement in this trial will involve:

Recruitment into the trial will take place within 24 hours of presentation to Frenchay Hospital.
If your patient agrees to enrol they will be given a course of tablets to take over the next 50 days. They may be given Vitamin C 500mg or the inactive placebo tablet, which will mean taking TWO CAPSULES PER DAY. The BRI pharmacist will hold the trial code and decide which tablet your patient is given.
The dose of Vitamin C is safe and will not affect other medications they are taking.
If your patient normally takes other Vitamins or multivitamins they should continue taking them.
They will continue to be treated by the orthopaedic team responsible for their wrist fracture. Involvement in the trial will not affect the type of treatment they receive.
At nine weeks from the time of the fracture your patient will be seen in the fracture clinic by the research doctor who will ask some questions and then perform some tests on their hands and fingers to look for symptoms and sign of CRPS.
Patients are not obliged to enter this study and are free to withdraw from the trial at any time without giving a reason. This will not affect any other treatment they may need.
Please feel free to contact us for any other information.

INCLUSION CRITERIA:

1. Over 50 years of age
2. Isolated unilateral closed fracture of the distal radius that is managed by cast immobilisation (+/-MUA) (+/-percutaneous wire fixation)

EXCLUSION CRITERIA:

1. Patients with any other ipsilateral upper limb injury.
2. Patients with any contra lateral upper limb injury. The contra lateral arm is used as an internal control in the study and any injury would affect the validity of this method.
3. Patients with dementia or who are unable to fully co-operate with the assessment are excluded as the assessments of pain and dolorimetry rely on patient's subjective response to a stimulus.
4. Patients with pre existing hand pathology that would affect the measurements (i.e. rheumatoid arthritis, severe Dupuytren's contracture etc.) are excluded, as this would compromise the validity of comparing the patients injured and uninjured hand. Conditions that would alter the patients pain threshold or finger movement would affect the validity of the assessment method.

5. Patients currently taking a therapeutic dose of Vitamin C on medical grounds.
6. Patients with fractures treated with operative fixation. Internal fixation requires significant tissue dissection and risks injury to small cutaneous nerves that may prejudice pain responses. External fixators may similarly cause cutaneous nerve injury and restrict tendon movement thus potentially affecting finger stiffness. (percutaneous wire fixation is permitted)

In the event of any difficulty or problems you can contact

Mr Andrew McBride MRCS(Ed)
Clinical Research Fellow
Department of Orthopaedic & Trauma Surgery
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Bristol
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Version 4 January 2004

9.4 APPENDIX 4

Trial proforma

Vitamin C/CRPS Trial Proforma

University of BRISTOL

First Visit

Patient Details

Patient Trial No.

Telephone: Home _____
Work _____
Mobile_____

DOB Age

Sex: Male ☐ Female ☐

Occupation

Smoker Yes ☐ No ☐

Injury

Date Time

Injured Wrist Left ☐ Right ☐ Frykman

Dominant Hand Yes ☐ No ☐

Treatment Date _____ Time_____

Initial Reduction None ☐ MUA ☐

Anaesthetic Biers block GA Sedation Haematoma block None

No of Remanipulations 0 1 2 3 4 K-Wires ☐

Pre-existing ipsilateral or contralateral upper limb pathology YES ☐

Currently taking Vitamin supplements YES ☐

Patient Trial No. ☐

Second Visit

Days post 1st reduction _____

Removal of POP date _____

No. of days immobilised _____

Plaster problems? Yes ☐ No ☐

Physiotherapy Yes ☐ No ☐

Physio started on: _____

Trial medications completed? Yes ☐ No ☐

Pill bottle returned? Empty ☐ Capsules remaining ☐

Patient Trial No. ☐

Pain Assessment

Spontaneous Pain Yes ☐ No ☐

On exercise Yes ☐ No ☐

Allodynia Yes ☐ No ☐

McGill Pain Assessment

	None	Mild	Moderate	Severe
Throbbing				
Shooting				
Stabbing				
Sharp				
Cramping				
Gnawing				
Hot-burning				
Aching				
Heavy				
Tender				
Splitting				
Tiring-exhausting				
Sickening				
Fearful				
Punishing-cruel				

Visual Analogue Score

NO PAIN |_____| SEVERE PAIN

Present Pain Intensity

0 No pain
1 Mild
2 Discomforting
3 Distressing
4 Horrible
5 Excruciating

Trophic Changes

Nail Growth Yes ☐ No ☐
Hair Colour/Growth Yes ☐ No ☐

Patient Trial No. ☐

Function

	Grip	Fine Control
Full		
Slight Restriction		
Severe Restriction		
Tremor		

Finger Stiffness

Present Yes ☐ No ☐

Daily Yes ☐ No ☐

am ☐ pm ☐ all day ☐

Vasomotor Instability

Have you noticed any changes in the appearance of your hand compared to the other recently, and if so, what changes exactly?

Have you noticed any changes in the colour of your hand recently, and if so what?

Has your hand felt any different from the other hand recently, since the accident, and if so, in what way?

Has the temperature of your hand felt in any way different from the other hand recently, and if so in what way?

Has your hand been bluer than the other hand recently, or bluer than it was before the accident and if so under what circumstances?

Has your hand been redder than the other hand recently, or redder than it was before the accident and if so under what circumstances?

Has your hand felt warmer than the other hand recently, or warmer than it did before the accident and if so under what circumstances?

Has your hand felt cooler than the other hand recently, or cooler than it did before the accident and if so under what circumstances?

Has your hand responded differently to changes in environmental temperature recently, and if so in what way?

Have you noticed you hand going red and warm in a hot environment or blue and cold in a cool environment?

Does your hand sweat or perspire more than it used to or more than the other side recently?

Clinical Findings

Swelling Yes ☐ No ☐

Colour Red ☐ Blue ☐ White ☐ Normal ☐

Sweating Yes ☐ No ☐

Skin Changes Yes ☐ No ☐

Nail Changes Yes ☐ No ☐

Hair Growth Yes ☐ No ☐

Others

Dolorimetry

	Fracture side					Control				
	MCPJ	PP	PIPJ	MP	DIPJ	MCPJ	PP	PIPJ	MP	DIPJ
INDEX										
MIDDLE										
RING										
LITTLE										

Patient Trial No. [ ]

Index Finger Swelling Ratio [ ]

	Test	Control
1		
2		
3		
Mean		

Grip Strength Ratio [ ]

	Test	Control
1		
2		
3		
Mean		

Finger Movement

Fracture side					Control			
	INDEX	MIDDLE	RING	LITTLE	INDEX	MIDDLE	RING	LITTLE
MCPJ								
PIPJ								
DIPJ								

VMI TOTAL [ ]

DOLOR RATIO [ ]

FINGER MOVEMENT [ ]

INDEX FINGER SWELLING [ ]

9.5 APPENDIX 5a

Dolorimetry measurement results from 19 control subjects.

Statistical significance between the right and left hand was assessed using a paired t test.

Finger Location	Right Mean	Standard Deviation	Left Mean	Standard Deviation	P Value
IMCPJ	2578.94	892.92	2847.36	866.90	0.084
IPP	2731.57	1060.42	2973.68	945.07	0.148
IPIPJ	3026.31	972.30	2942.10	970.28	0.619
IMP	3047.36	905.15	2931.57	866.70	0.429
IDIPJ	3257.89	1110.21	2942.10	906.34	0.098
MMCPJ	2515.78	941.19	2626.31	1097.89	0.579
MPP	2794.73	1011.85	3000	928.55	0.196
MPIPJ	2836.84	955.80	2805.26	1058.02	0.832
MMP	3352.63	962.84	3421.05	763.45	0.575
MDIPJ	3089.47	1009.89	3247.36	964.00	0.230
RMCPJ	2642.10	859.14	2794.73	827.62	0.322
RPP	2742.10	818.74	2942.10	962.81	0.036
RPIPJ	2694.73	1010.76	2868.42	942.25	0.359
RMP	3415.78	947.66	3178.94	813.48	0.153
RDIPJ	3115.78	958.73	3184.21	850.66	0.600
LMCPJ	2468.42	936.92	2668.42	935.14	0.151
LPP	2763.15	911.78	2878.94	936.64	0.315
LPIPJ	2952.63	834.24	2836.84	903.21	0.414
LMP	2742.10	919.73	2910.52	893.74	0.311
LDIPJ	2857.89	905.11	2763.15	905.66	0.382

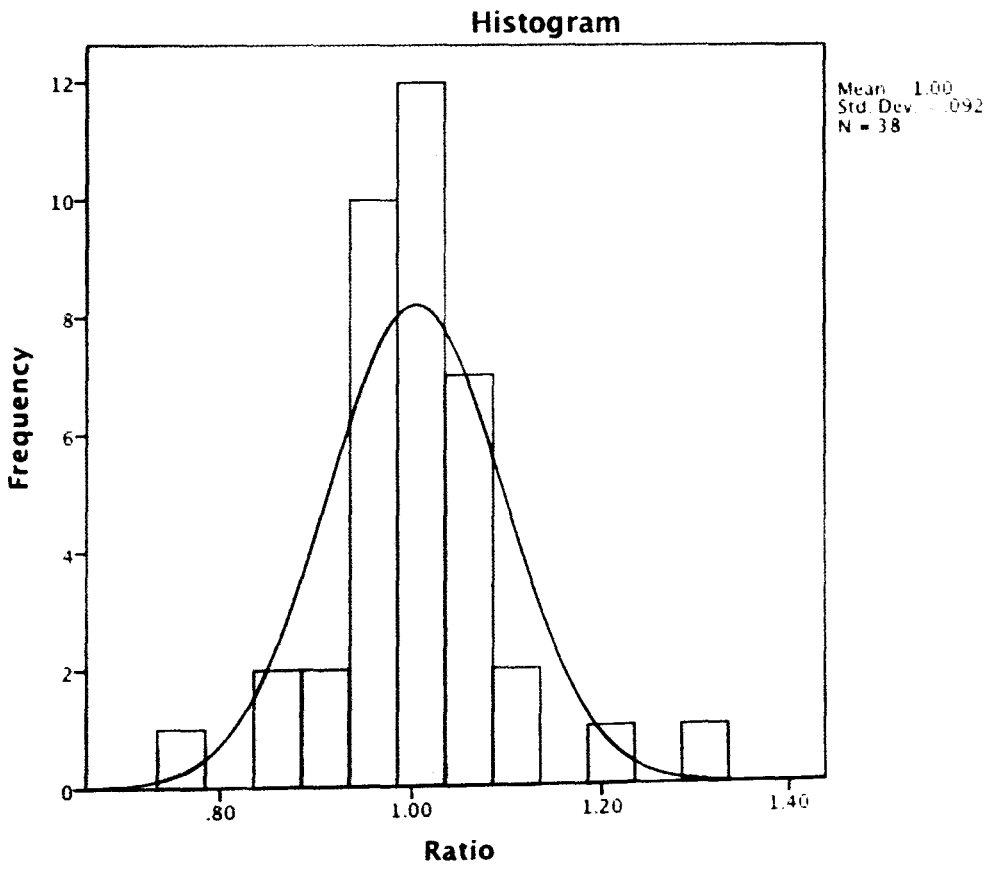
9.6 APPENDIX 5b

Dolorimetry ratio results in 19 control subjects

Patient No.	Age	Sex	Ratio Right:Left	Ratio Left:Right
1	70.5	F	0.93	1.07
2	59.11	F	0.76	1.32
3	77	F	1.03	0.97
4	58.11	M	1	1
5	53.1	F	1.03	0.97
6	57.9	F	0.99	1.01
7	55.1	M	0.96	1.04
8	57.8	M	1.04	0.96
9	62.1	F	1.02	0.98
10	67.8	M	1.05	0.96
11	75.2	M	0.99	1.01
12	67.1	F	0.88	1.13
13	76.11	F	0.9	1.11
14	78.1	F	0.96	1.05
15	56	F	0.94	1.06
16	57.1	F	0.99	1.01
17	57.2	M	0.98	1.02
18	81.8	F	1.19	0.84
19	76.1	F	1.05	0.96

Control group dolorimetry ratio data statistics and histogram

N	**Count**	38
	Missing	0
Mean		1.0042
Std. Error of Mean		.01499
Median		1.0000
Mode		.96
Std. Deviation		.09240
Variance		.009
Skewness		.676
Std. Error of Skewness		.383
Kurtosis		3.833
Std. Error of Kurtosis		.750
Range		.56
Minimum		.76
Maximum		1.32
Sum		38.16



9.7 APPENDIX 5c

Control group reliability study - dolorimetry scores for individual finger sites

right hand

Finger Position	Mean Right 1st	Mean Right 2nd	Standard Error of Measurement	Intraclass Coefficient	95% Ci
IMCPJ	2733.33	2925.00	711.21	0.500	-0.073 to 0.825
IPP	2916.67	3216.67	555.35	0.796	0.433 to 0.937
IPIPJ	3283.33	3133.33	403.21	0.888	0.657 to 0.966
IMP	3308.33	3241.67	301.95	0.930	0.776 to 0.979
IDIPJ	3475.00	3625.00	476.21	0.831	0.515 to 0.948
MMCPJ	2683.33	2383.33	362.19	0.905	0.704 to 0.972
MMP	2975.00	2941.67	413.18	0.895	0.808 to 0.984
MPIPJ	2908.33	2775.00	437.78	0.854	0.571 to 0.956
MMP	3383.33	3325.00	496.24	0.790	0.421 to 0.935
MDIPJ	3358.33	3216.67	418.43	0.899	0.687 to 0.970
RMCPJ	2858.33	2841.67	572.46	0.476	-0.105 to 0.814
RPP	2916.67	2700.00	420.71	0.785	0.411 to 0.973
RPIPJ	2800.00	2675.00	242.46	0.955	0.850 to 0.987
RMP	3350.00	3233.33	286.53	0.930	0.776 to 0.979
RDIPJ	3150.00	3158.33	292.86	0.942	0.811 to 0.983
LMCPJ	2833.33	2808.33	491.53	0.844	0.545 to 0.952
LPP	3075.00	3033.33	311.33	0.931	0.779 to 0.980
LPIPJ	3166.67	3266.67	167.06	0.978	0.924 to 0.933
LMP	2900.00	2691.67	260.05	0.955	0.851 to 0.987
LDIPJ	2975.00	2875.00	301.18	0.935	0.790 to 0.981

Control group reliability study - dolorimetry scores for individual finger sites left hand

Finger Position	Mean Left 1st	Mean Left 2nd	Standard Error of Measurement	Intraclass Coefficient	95% Ci
IMCPJ	2983.33	2841.67	389.04	0.895	0.676 to 0.968
IPP	3216.67	3225.00	313.57	0.932	0.783 to 0.980
IPIPJ	3208.33	3266.67	579.28	0.709	0.256 to 0.906
IMP	3175.00	3350.00	475.66	0.831	0.515 to 0.948
IDIPJ	3050.00	2575.00	858.50	0.517	-0.050 to 0.832
MMCPJ	2791.67	2675.00	530.72	0.825	0.501 to 0.946
MMP	3183.33	2941.67	390.83	0.859	0.583 to 0.957
MPIPJ	2958.33	3166.67	376.28	0.900	0.691 to 0.970
MMP	3516.67	3316.67	364.11	0.888	0.659 to 0.967
MDIPJ	3491.67	3316.67	368.16	0.910	0.718 to 0.973
RMCPJ	3066.67	3316.67	788.49	0.163	-0.429 to 0.657
RPP	3100.00	3016.67	342.04	0.908	0.712 to 0.972
RPIPJ	3166.67	2950.00	455.74	0.868	0.606 to 0.960
RMP	3325.00	2925.00	425.93	0.830	0.513 to 0.948
RDIPJ	3375.00	3225.00	188.64	0.970	0.901 to 0.991
LMCPJ	3083.33	3025.00	465.77	0.732	0.302 to 0.915
LPP	3183.33	3108.33	439.04	0.855	0.574 to 0.956
LPIPJ	2958.33	3033.33	463.77	0.876	0.627 to 0.963
LMP	3025.00	2866.67	225.56	0.958	0.862 to 0.988
LDIPJ	2958.33	3008.33	459.81	0.854	0.569 to 0.956

Control group reliability study - dolorimetry ratios (right: left) for individual finger sites

Finger Position	Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
IMCPJ	0.92	1.03	0.36	0.353	-0.249 to 0.758
IPP	0.91	1.00	0.21	0.666	0.179 to 0.891
IPIPJ	1.02	0.96	0.25	0.561	0.012 to 0.850
IMP	1.04	0.97	0.26	0.527	-0.037 to 0.836
IDIPJ	1.14	1.41	1.27	-0.079	-0.606 to 0.496
MMCPJ	0.96	0.89	0.25	0.718	0.274 to 0.910
MMP	0.93	1.00	0.22	0.712	0.263 to 0.908
MPIPJ	0.98	0.87	0.17	0.699	0.283 to 0.903
MMP	0.96	1.00	0.09	0.771	0.380 to 0.928
MDIPJ	0.96	0.97	0.19	0.408	-0.187 to 0.784
RMCPJ	0.93	0.86	0.30	0.298	-0.305 to 0.731
RPP	0.94	0.90	0.19	0.360	-0.241 to 0.761
RPIPJ	0.88	0.91	0.11	0.912	0.724 to 0.974
RMP	1.01	1.11	0.26	0.680	0.204 to 0.896
RDIPJ	0.93	0.98	0.13	0.970	0.901 to 0.991
LMCPJ	0.92	0.93	0.23	0.629	0.117 to 0.877
LPP	0.97	0.98	0.33	0.493	-0.083 to 0.822
LPIPJ	1.07	1.08	0.25	0.442	-0.147 to 0.800
LMP	0.96	0.94	0.11	0.509	-0.061 to 0.829
LDIPJ	1.00	0.96	0.32	0.885	0.649 to 0.965

Control group reliability study - dolorimetry scores for whole fingers right hand

Finger	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	15716.67	16141.67	1283.87	0.910	0.719 to 0.973
Middle	15308.33	14641.67	1032.79	0.960	0.868 to 0.988
Ring	15075.00	14608.33	770.44	0.968	0.892 to 0.991
Little	15050.00	14575.00	571.61	0.985	0.950 to 0.996

Control group reliability study - dolorimetry scores for whole fingers left hand

Finger	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	15716.67	16141.67	1131.94	0.942	0.812 to 0.983
Middle	15308.33	14641.67	994.09	0.961	0.872 to 0.989
Ring	15075.00	14608.33	1131.86	0.936	0.793 to 0.981
Little	15050.00	14575.00	755.92	0.974	0.912 to 0.992

Control group reliability study - dolorimetry ratio (right: left) for whole fingers

Finger	Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	1.02	1.07	0.11	0.626	0.111 to 0.876
Middle	0.96	0.95	0.10	0.718	0.273 to 0.910
Ring	0.94	0.95	0.09	0.671	0.188 to 0.893
Little	0.93	0.96	0.06	0.797	0.437 to 0.937

Control group reliability study - dolorimetry scores for individual positions right hand

Joint	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	11108.33	10958.33	1447.56	0.822	0.492 to 0.945
PPs	11883.33	11891.67	626.73	0.977	0.922 to 0.993
PIPJs	12158.33	11850.00	659.28	0.970	0.899 to 0.991
MPs	12941.67	12491.67	720.03	0.970	0.899 to 0.991
DIPJs	12958.33	12875.00	702.70	0.972	0.906 to 0.992

Control group reliability study - dolorimetry scores for individual positions left hand

Joint	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	11925.00	11858.33	662.32	0.959	0.865 to 0.988
PPs	12683.33	12291.67	811.14	0.954	0.848 to 0.986
PIPJs	12291.67	12416.67	920.47	0.954	0.849 to 0.987
MPs	13041.67	12458.33	642.53	0.971	0.902 to 0.991
DIPJs	12875.00	12125.00	1257.72	0.910	0.718 to 0.973

Control group reliability study - dolorimetry ratios (right: left) for individual positions

Joint	Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	0.94	0.94	0.16	0.579	0.039 to 0.857
PPs	0.93	0.97	0.05	0.823	0.496 to 0.946
PIPJs	1.01	0.97	0.11	0.764	0.366 to 0.926
MPs	0.99	1.01	0.07	0.855	0.573 to 0.956
DIPJs	1.01	1.08	0.13	0.402	-0.194 to 0.731

Control group reliability study - dolorimetry scores for the whole of right hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
36630.00	36040.00	1234.99	0.852	0.664 to 0.939

Control group reliability study - dolorimetry scores for the whole of left hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
37690.00	36690.00	1591.09	0.572	0.184 to 0.805

Control group reliability study - dolorimetry ratios for the whole hand (right: left)

Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
1.01	1.02	0.08	0.893	0.672 to 0.968

9.8 APPENDIX 5d

Study group reliability study - dolorimetry scores for individual finger sites

fracture side

Finger Position	Mean 1st	Mean 2nd	Standard Error of Measurement	Intraclass Coefficient	95% Ci
IMCPJ	1810	1560	292.76	0.919	0.708 to 0.979
IPP	2160	2070	126.96	0.990	0.962 to 0.998
IPIPJ	1770	1730	215.39	0.967	0.875 to 0.992
IMP	2330	2190	110.82	0.994	0.970 to 0.999
IDIPJ	2040	2040	184.70	0.979	0.919 to 0.995
MMCPJ	1690	1630	268.29	0.937	0.770 to 0.984
MMP	2030	1920	418.03	0.851	0.512 to 0.961
MPIPJ	1650	1650	218.54	0.958	0.840 to 0.989
MMP	2160	1990	206.71	0.976	0.905 to 0.994
MDIPJ	2100	2050	315.21	0.926	0.731 to 0.981
RMCPJ	1830	1740	167.51	0.978	0.913 to 0.994
RPP	1980	1960	263.80	0.956	0.835 to 0.989
RPIPJ	1570	1560	139.75	0.983	0.934 to 0.996
RMP	2100	2170	206.71	0.980	0.920 to 0.995
RDIPJ	1750	1730	99.46	0.990	0.962 to 0.998
LMCPJ	1330	1380	203.38	0.911	0.685 to 0.997
LPP	1820	1750	149.19	0.973	0.896 to 0.993
LPIPJ	1550	1570	122.51	0.977	0.912 to 0.994
LMP	1530	1480	238.15	0.912	0.687 to 0.977
LDIPJ	1670	1670	251.22	0.938	0.772 to 0.984

Study group reliability study - dolorimetry scores for individual finger sites control hand

Finger Position	Mean 1st	Mean 2nd	Standard Error of Measurement	Intraclass Coefficient	95% Ci
IMCPJ	2330	2090	223.17	0.953	0.825 to 0.988
IPP	2760	2730	374.10	0.917	0.703 to 0.979
IPIPJ	2590	2600	195.68	0.982	0.931 to 0.996
IMP	3170	3060	361.11	0.938	0.772 to 0.984
IDIPJ	2450	2510	211.40	0.980	0.923 to 0.995
MMCPJ	3250	3260	208.35	0.982	0.929 to 0.995
MMP	2850	2780	335.65	0.936	0.764 to 0.984
MPIPJ	3040	3050	231.61	0.965	0.866 to 0.991
MMP	3270	3230	171.28	0.986	0.994 to 0.996
MDIPJ	2950	2740	200.00	0.978	0.915 to 0.995
RMCPJ	2930	2720	457.01	0.894	0.632 to 0.973
RPP	2840	2860	319.37	0.941	0.781 to 0.985
RPIPJ	2920	2960	367.55	0.925	0.730 to 0.981
RMP	3240	3000	271.45	0.961	0.853 to 0.990
RDIPJ	2720	2660	190.16	0.976	0.905 to 0.994
LMCPJ	2540	2480	176.19	0.968	0.878 to 0.992
LPP	2970	2880	212.40	0.972	0.891 to 0.993
LPIPJ	2860	2940	141.87	0.988	0.954 to 0.997
LMP	3090	3020	233.81	0.968	0.878 to 0.992
LDIPJ	2620	2520	143.07	0.985	0.943 to 0.996

Study group reliability study - dolorimetry ratios (right: left) for individual finger sites

Finger Position	Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
IMCPJ	0.77	0.74	0.13	0.884	0.602 to 0.970
IPP	0.78	0.75	0.13	0.893	0.631 to 0.972
IPIPJ	0.68	0.66	0.12	0.870	0.563 to 0.966
IMP	0.73	0.71	0.13	0.861	0.538 to 0.964
IDIPJ	0.83	0.81	0.07	0.950	0.813 to 0.987
MMCPJ	0.52	0.50	0.09	0.847	0.501 to 0.960
MMP	0.71	0.69	0.18	0.703	0.175 to 0.917
MPIPJ	0.54	0.54	0.09	0.918	0.706 to 0.979
MMP	0.66	0.61	0.06	0.952	0.820 to 0.988
MDIPJ	0.71	0.74	0.13	0.825	0.442 to 0.953
RMCPJ	0.62	0.63	0.17	0.535	-0.099 to 0.860
RPP	0.69	0.68	0.09	0.920	0.714 to 0.980
RPIPJ	0.53	0.52	0.11	0.832	0.462 to 0.956
RMP	0.64	0.72	0.13	0.909	0.677 to 0.977
RDIPJ	0.64	0.65	0.06	0.957	0.836 to 0.989
LMCPJ	0.52	0.55	0.10	0.830	0.455 to 0.955
LPP	0.61	0.60	0.08	0.914	0.692 to 0.978
LPIPJ	0.54	0.53	0.03	0.991	0.966 to 0.998
LMP	0.49	0.49	0.11	0.748	0.265 to 0.931
LDIPJ	0.63	0.66	0.13	0.928	0.740 to 0.982

Study group reliability study - dolorimetry scores for whole fingers affected hand

Finger	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	10110.00	9590.00	438.63	0.994	0.937 to 0.999
Middle	9630.00	9240.00	648.35	0.984	0.937 to 0.996
Ring	9230.00	9160.00	528.98	0.989	0.958 to 0.997
Little	7900.00	7850.00	449.11	0.985	0.940 to 0.996

Study group reliability study - dolorimetry scores for whole fingers control hand

Finger	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	13300.00	12990.00	920.21	0.979	0.917 to 0.995
Middle	15360.00	15060.00	547.90	0.993	0.971 to 0.998
Ring	14650.00	14200.00	527.68	0.992	0.969 to 0.998
Little	14080.00	13840.00	522.73	0.991	0.966 to 0.998

Study group reliability study - dolorimetry ratio (affected: control) for whole fingers

Finger	Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	0.75	0.72	0.06	0.964	0.863 to 0.991
Middle	0.61	0.60	0.04	0.970	0.885 to 0.992
Ring	0.60	0.62	0.04	0.974	0.901 to 0.994
Little	0.55	0.56	0.04	0.967	0.875 to 0.992

Study group reliability study - dolorimetry scores for individual positions affected hand

Joint	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	6660.00	6310.00	381.32	0.987	0.949 to 0.997
PPs	7990.00	7700.00	390.61	0.992	0.967 to 0.998
PIPJs	6540.00	6510.00	479.95	0.982	0.930 to 0.996
MPs	8120.00	7830.00	323.75	0.995	0.979 to 0.999
DIPJs	7560.00	7490.00	512.60	0.983	0.934 to 0.996

Study group reliability study - dolorimetry scores for individual positions control hand

Joint	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	11050.00	10550.00	605.57	0.981	0.924 to 0.995
PPs	11420.00	11250.00	541.72	0.988	0.951 to 0.997
PIPJs	11410.00	11550.00	672.56	0.982	0.929 to 0.995
MPs	12770.00	12310.00	402.96	0.994	0.976 to 0.999
DIPJs	10740.00	10430.00	478.88	0.990	0.961 to 0.998

Study group reliability study - dolorimetry ratios (affected: control) for individual positions

Joint	Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	0.58	0.57	0.04	0.952	0.819 to 0.988
PPs	0.68	0.67	0.04	0.976	0.906 to 0.994
PIPJs	0.57	0.56	0.06	0.936	0.765 to 0.984
MPs	0.61	0.60	0.04	0.970	0.886 to 0.993
DIPJs	0.70	0.70	0.06	0.943	0.788 to 0.985

Study group reliability study - dolorimetry scores for the whole of affected hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
57390.00	56090.00	1213.80	0.996	0.984 to 0.999

Study group reliability study - dolorimetry scores for the whole of control hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
36870.00	35690.00	833.20	0.997	0.988 to 0.999

Study group reliability study - dolorimetry ratios for the whole hand

Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
0.62	0.61	0.01	0.992	0.967 to 0.998

9.9 APPENDIX 6a

Joint movement measurements in 19 control subjects

Statistical significance between the right and left hand was assessed using a paired t test.

Joint	Right Mean	Standard Deviation	Left Mean	Standard Deviation	P-Value
IMCPJ	72.05	8.64	74.32	7.17	0.283
IPIPJ	105.63	6.69	104.37	7.85	0.353
IDIPJ	67.89	11.43	70.26	10.29	0.245
MMCPJ	79.47	6.41	79.47	4.38	1.000
MPIPJ	103.05	6.49	104.47	5.39	0.363
MDIPJ	74.26	13.17	76.00	10.01	0.455
RMCPJ	81.68	5.68	80.16	6.44	0.260
RPIPJ	102.95	6.26	101.89	6.31	0.465
RDIPJ	70.42	10.77	70.68	14.33	0.917
LMCPJ	89.16	7.33	83.95	6.30	**0.002**
LPIPJ	97.00	10.68	95.16	7.68	0.469
LDIPJ	78.58	11.76	78.42	12.70	0.960

Joint	Right Mean	Standard Deviation	Left Mean	Standard Deviation	P-Value
Hand Total	1022.16	53.52	1019.16	56.85	0.682

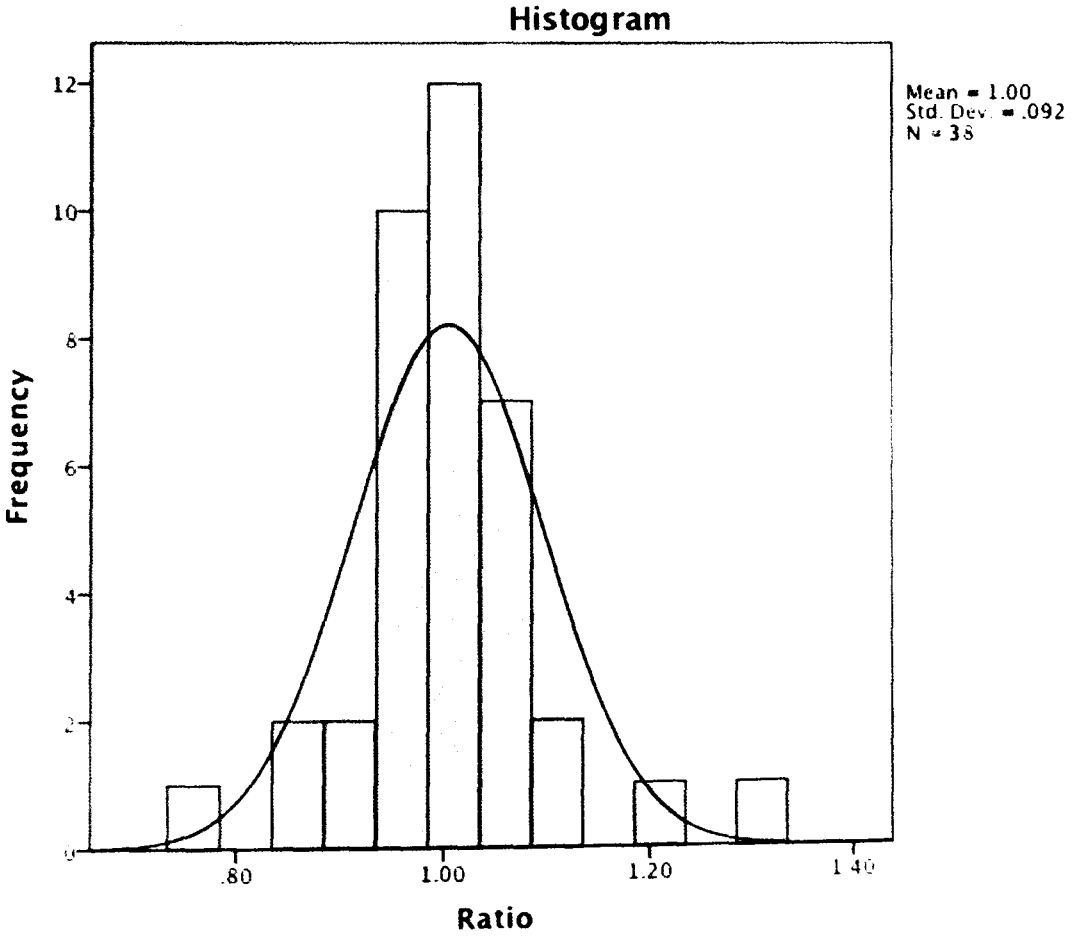
9.10 APPENDIX 6b

Cumulative finger movement differences (in degrees) for 19 control subjects.

Patient No	Age	Sex	Right – Left	Left _ Right
1	70.5	F	15	-15
2	59.11	F	14	-14
3	77	F	71	-71
4	58.11	M	9	-9
5	53.1	F	17	-17
6	57.9	F	12	-12
7	55.1	M	36	-36
8	57.8	M	22	-22
9	62.1	F	1	-1
10	67.8	M	31	-31
11	75.2	M	53	-53
12	67.1	F	5	-5
13	76.11	F	11	-11
14	78.1	F	50	-50
15	56	F	1	-1
16	57.1	F	7	-7
17	57.2	M	46	-46
18	81.8	F	19	-19
19	76.1	F	35	-35

Control group cumulative finger movement difference data and histogram

N	**Count**	38
	Missing	0
Mean		-.41
Std. Error of Mean		5.171
Median		-1.00
Mode		-1[a]
Std. Deviation		31.455
Variance		989.414
Skewness		.038
Std. Error of Skewness		.388
Kurtosis		-.001
Std. Error of Kurtosis		.759
Range		142
Minimum		-71
Maximum		71
Sum		-15



9.11APPENDIX 6c

Control group reliability study – finger stiffness values for individual finger sites right hand

Finger Position	Mean 1st	Mean 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
IMCPJ	74.17	74.25	3.84	0.898	0.686 to 0.970
IPIPJ	105.25	104.00	4.26	0.785	0.410 to 0.933
IDIPJ	69.92	68.50	4.43	0.919	0.743 to 0.976
MMCPJ	80.83	80.92	4.63	0.733	0.302 to 0.915
MPIPJ	102.50	99.42	4.54	0.775	0.389 to 0.930
MDIPJ	76.08	74.75	2.73	0.980	0.931 to 0.994
RMCPJ	82.42	84.25	4.09	0.732	0.301 to 0.915
RPIPJ	102.33	99.33	3.03	0.864	0.595 to 0.959
RDIPJ	72.50	70.25	2.02	0.984	0.944 to 0.995
LMCPJ	91.25	92.25	2.36	0.898	0.684 to 0.969
LPIPJ	95.25	95.25	1.90	0.981	0.935 to 0.994
LDIPJ	82.08	81.50	2.16	0.975	0.917 to 0.993

Control group reliability study – finger stiffness values for individual finger sites left hand

Finger Position	Mean 1st	Mean 2nd	Standard Deviation of Error of Measurement	Intraclass Coefficient	95% CI
IMCPJ	76.50	77.08	3.63	0.855	0.574 to 0.956
IPIPJ	103.33	102.58	2.34	0.949	0.834 to 0.985
IDIPJ	73.75	72.58	2.56	0.964	0.880 to 0.989
MMCPJ	79.92	81.50	3.18	0.837	0.582 to 0.950
MPIPJ	103.50	102.50	2.11	0.873	0.617 to 0.962
MDIPJ	76.50	77.17	3.18	0.943	0.815 to 0.983
RMCPJ	79.00	80.58	3.71	0.835	0.524 to 0.950
RPIPJ	102.58	102.75	2.82	0.838	0.532 to 0.951
RDIPJ	73.50	75.58	2.38	0.981	0.936 to 0.995
LMCPJ	84.00	83.50	2.06	0.923	0.757 to 0.977
LPIPJ	94.50	95.00	1.02	0.986	0.952 to 0.996
LDIPJ	77.67	78.00	1.26	0.995	0.984 to 0.999

Control group reliability study – finger stiffness values for whole fingers right hand

Finger	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	249.33	246.75	4.96	0.944	0.819 to 0.984
Middle	259.42	255.08	6.82	0.872	0.617 to 0.961
Ring	257.25	253.83	6.14	0.913	0.728 to 0.974
Little	268.58	269.00	3.69	0.968	0.894 to 0.991

Control group reliability study - finger stiffness values for whole fingers left hand

Finger	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	253.58	252.25	5.26	0.963	0.793 to 0.981
Middle	259.92	261.17	4.08	0.957	0.857 to 0.987
Ring	255.08	258.92	6.00	0.929	0.774 to 0.979
Little	256.17	256.50	2.83	0.980	0.933 to 0.966

Control group reliability study - finger stiffness values for individual positions right hand

Joint	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	328.67	331.67	8.15	0.923	0.755 to 0.977
PIPJs	405.33	398.00	5.23	0.947	0.829 to 0.985
DIPJs	300.58	295.00	5.99	0.989	0.964 to 0.997

Control group reliability study - finger stiffness values for individual positions left hand

Joint	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	319.42	322.67	6.56	0.951	0.840 to 0.986
PIPJs	403.92	402.83	4.07	0.952	0.844 to 0.986
DIPJs	301.42	303.33	6.28	0.988	0.958 to 0.996

Control group reliability study - finger stiffness values for the whole of right hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
1034.58	1024.67	10.25	0.963	0.877 to 0.989

Control group reliability study - finger stiffness values for the whole of left hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
1024.75	1028.83	8.17	0.997	0.987 to 0.999

Control group reliability study - finger stiffness values differences for the whole hand (right - left)

Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
4.67	-4.17	18.84	0.687	0.216 to 0.899

9.12 APPENDIX 6d

Study group reliability study – finger stiffness values for individual finger sites affected hand

Finger Position	Mean 1st	Mean 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
IMCPJ	60.40	59.80	1.76	0.984	0.938 to 0.996
IPIPJ	79.30	77.90	3.04	0.956	0.832 to 0.989
IDIPJ	47.40	46.20	1.97	0.988	0.954 to 0.997
MMCPJ	64.50	63.80	1.71	0.989	0.956 to 0.997
MPIPJ	84.10	84.00	1.57	0.993	0.971 to 0.998
MDIPJ	54.50	53.70	2.76	0.989	0.956 to 0.997
RMCPJ	63.10	62.90	0.91	0.998	0.933 to 1.000
RPIPJ	84.00	83.80	1.64	0.984	0.935 to 0.996
RDIPJ	46.60	47.10	1.61	0.993	0.973 to 0.998
LMCPJ	63.00	63.80	2.67	0.983	0.934 to 0.996
LPIPJ	76.00	76.60	2.68	0.974	0.898 to 0.993
LDIPJ	48.10	47.60	1.81	0.987	0.948 to 0.997

Study group reliability study – finger stiffness values for individual finger sites control hand

Finger Position	Mean 1st	Mean 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
IMCPJ	72.20	72.30	1.77	0.949	0.809 to 0.987
IPIPJ	99.80	99.30	2.23	0.960	0.849 to 0.990
IDIPJ	62.70	61.90	1.36	0.994	0.976 to 0.999
MMCPJ	79.40	79.30	2.39	0.868	0.557 to 0.965
MPIPJ	102.50	100.30	2.47	0.943	0.788 to 0.986
MDIPJ	71.50	71.00	1.99	0.991	0.962 to 0.998
RMCPJ	81.50	81.50	0.92	0.993	0.971 to 0.998
RPIPJ	98.50	97.90	1.66	0.984	0.936 to 0.996
RDIPJ	61.60	60.60	1.24	0.995	0.979 to 0.999
LMCPJ	80.30	80.40	1.62	0.981	0.926 to 0.995
LPIPJ	90.30	89.20	1.27	0.994	0.977 to 0.999
LDIPJ	66.00	66.20	1.36	0.984	0.937 to 0.996

Study group reliability study – finger stiffness values for whole fingers affected hand

Finger	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	187.10	183.90	4.54	0.971	0.887 to 0.993
Middle	203.10	201.50	4.13	0.992	0.968 to 0.998
Ring	193.70	193.80	3.21	0.991	0.963 to 0.998
Little	187.10	188.00	3.05	0.990	0.960 to 0.997

Study group reliability study - finger stiffness values for whole fingers control hand

Finger	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
Index	234.70	233.50	2.61	0.991	0.963 to 0.998
Middle	253.40	250.60	2.14	0.994	0.976 to 0.999
Ring	241.60	240.00	1.90	0.996	0.983 to 0.999
Little	236.60	235.80	2.02	0.993	0.972 to 0.998

Study group reliability study - finger stiffness values for individual positions affected hand

Joint	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	251.00	250.30	2.98	0.998	0.992 to 1.000
PIPJs	323.40	322.30	4.14	0.994	0.987 to 0.999
DIPJs	196.60	194.60	3.60	0.998	0.991 to 0.999

Study group reliability study - finger stiffness values for individual positions control hand

Joint	Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
MCPJs	313.40	313.50	3.39	0.977	0.909 to 0.994
PIPJs	391.10	386.70	4.41	0.987	0.949 to 0.997
DIPJs	261.80	259.70	2.42	0.998	0.992 to 1.000

Study group reliability study - finger stiffness values for the whole of affected hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
771.00	767.20	5.17	0.997	0.989 to 0.999

Study group reliability study - finger stiffness values for the whole of control hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
966.30	959.90	3.92	0.997	0.987 to 0.999

Study group reliability study - finger stiffness values differences for the whole hand (affected – control)

Mean Ratio 1st	Mean Ratio 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
-195.30	-192.70	6.81	0.996	0.983 to 0.999

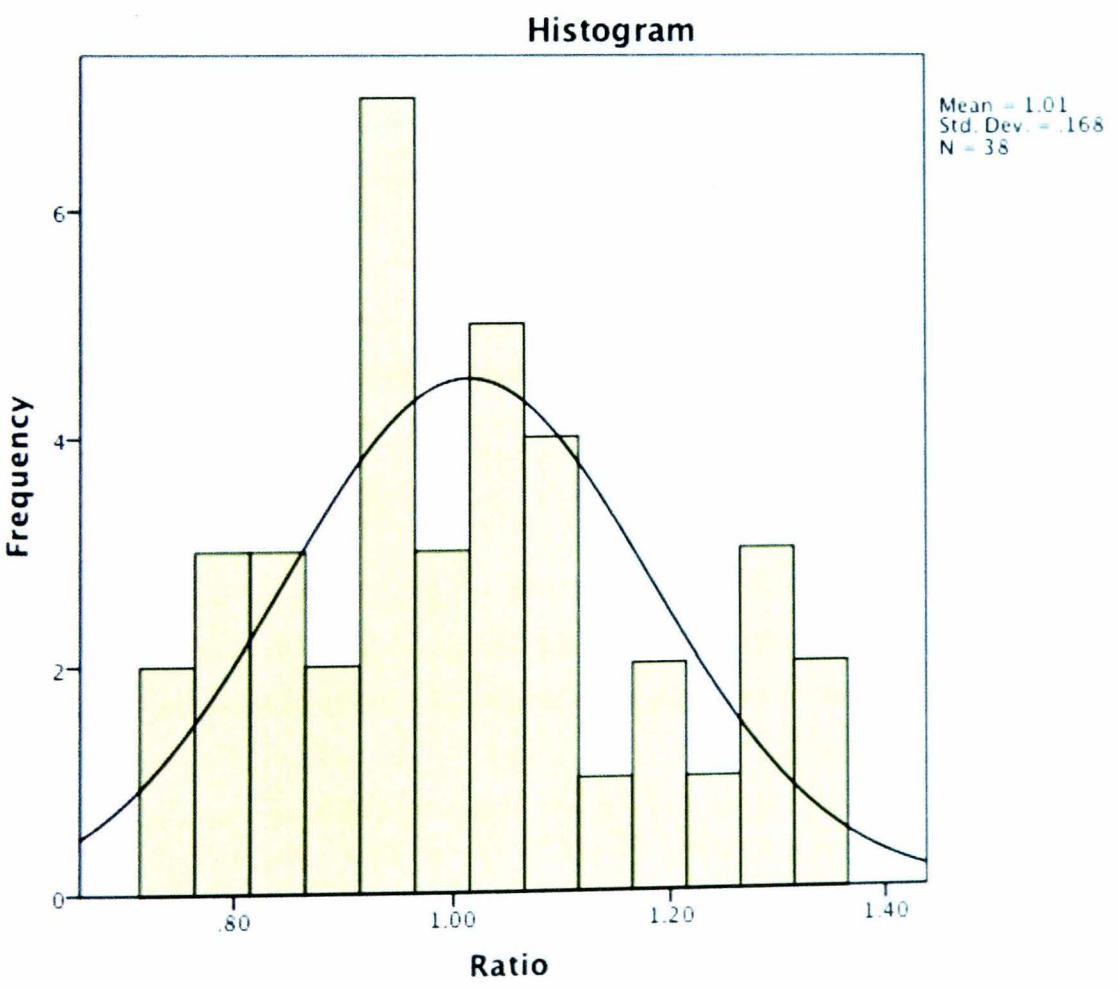
9.13 APPENDIX 7a

Control group index finger swelling normality measurements (mm) and ratios in 19 subjects

Pt No.	Age	Sex	Right index	Left Index	Ratio R:L	Ratio L:R
1	70.5	F	18.33	22	1.2	0.83
2	59.11	F	15.67	14.33	1.09	0.91
3	77	F	14.67	11.33	1.29	0.77
4	58.11	M	24.67	23.67	1.04	0.96
5	53.1	F	12.67	9.33	1.36	0.74
6	57.9	F	18	14	1.29	0.78
7	55.1	M	22.33	19.33	1.16	0.87
8	57.8	M	21	20	1.05	0.95
9	62.1	F	18.33	15	1.22	0.82
10	67.8	M	23	19.67	1.17	0.86
11	75.2	M	24	24.33	0.99	1.01
12	67.1	F	16.33	12.33	1.32	0.76
13	76.11	F	10	10.67	0.94	1.07
14	78.1	F	10.33	10	1.03	0.97
15	56	F	9.33	7.33	1.27	0.79
16	57.1	F	13.33	12.67	1.05	0.95
17	57.2	M	25.67	24	1.07	0.93
18	81.8	F	14.33	15	0.96	1.05
19	76.1	F	15	14	1.07	0.93

Index finger swelling ratio normality data and histogram

N	**Count**	38
	Missing	0
Mean		1.0137
Std. Error of Mean		.02721
Median		1.0000
Mode		1.05[a]
Std. Deviation		.16773
Variance		.028
Skewness		.325
Std. Error of Skewness		.383
Kurtosis		-.613
Std. Error of Kurtosis		.750
Range		.62
Minimum		.74
Maximum		1.36
Sum		38.52



9.14APPENDIX 7b

Control group reliability study - index finger swelling left hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
15.73	15.54	0.35	0.996	0.989 to 0.998

Control group reliability study - index finger swelling right hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
17.21	17.26	0.49	0.991	0.977 to 0.996

Control group reliability study - index finger swelling ratio (Right: Left)

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
1.12	1.14	0.06	0.803	0.557 to 0.919

9.15 APPENDIX 7c

Study group reliability study - index finger swelling affected hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
14.93	15.10	0.41	0.982	0.929 to 0.995

Study group reliability study - index finger swelling control hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
11.87	11.90	0.38	0.980	0.921 to 0.995

Study group reliability study - index finger swelling ratio (affected: control)

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
1.29	1.30	0.05	0.964	0.864 to 0.991

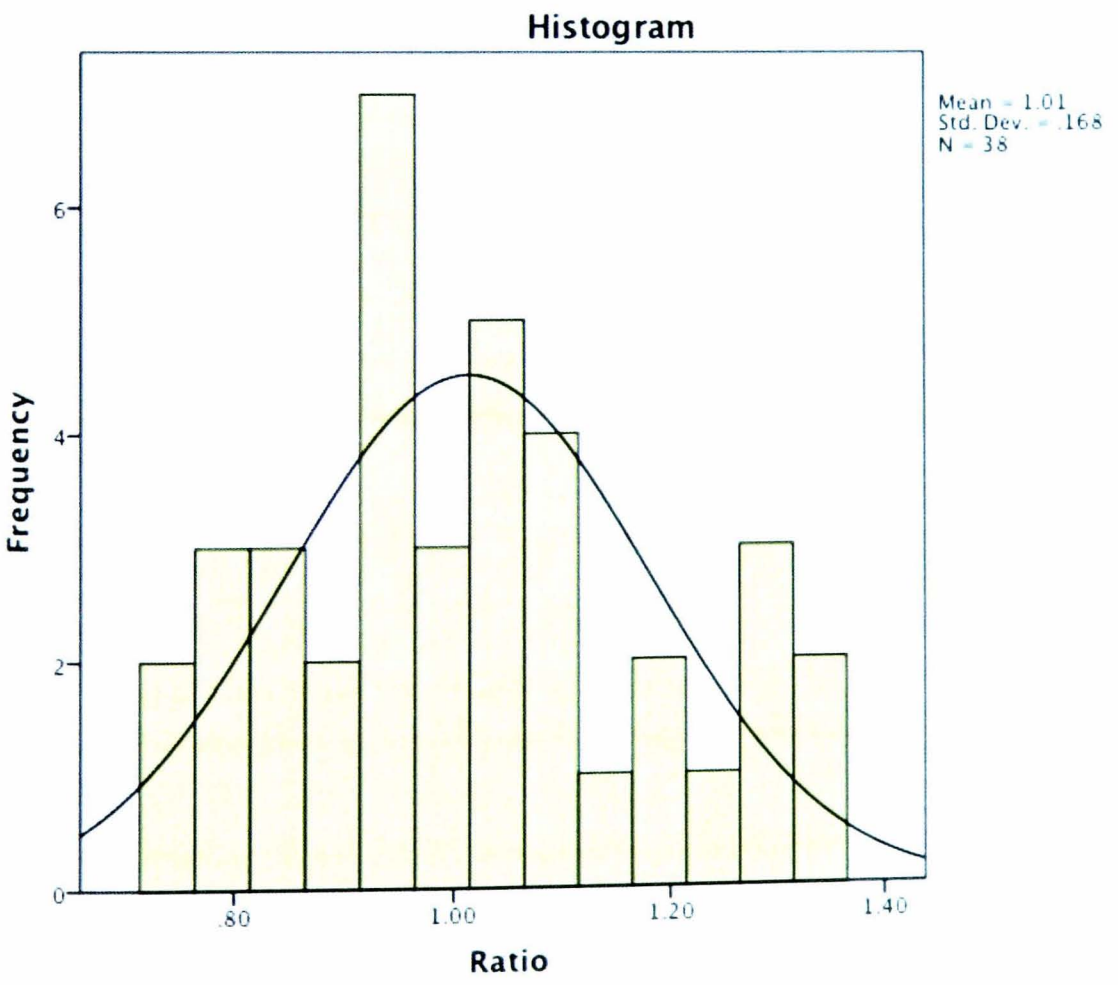
9.16APPENDIX 8a

Control group hand grip strength measurements and ratios in 19 subjects.

Pt No.	Age	Sex	Right	Left	Ratio R:L	Ratio L:R
1	70.5	F	42	42	1	1
2	59.11	F	30	31	0.97	1.03
3	77	F	21	19	1.11	0.9
4	58.11	M	40	38	1.05	0.95
5	53.1	F	20	17	1.18	0.85
6	57.9	F	26	20	1.3	0.77
7	55.1	M	39	42	0.93	1.08
8	57.8	M	52	58	0.9	1.12
9	62.1	F	32	33	0.97	1.03
10	67.8	M	25	20	1.25	0.8
11	75.2	M	44	43	1.02	0.98
12	67.1	F	22	24	0.92	1.09
13	76.11	F	18	14	1.29	0.78
14	78.1	F	22	20	1.1	0.91
15	56	F	25	22	1.09	0.88
16	57.1	F	24	20	1.2	0.83
17	57.2	M	34	33	1.03	0.97
18	81.8	F	16	18	0.89	1.13
19	76.1	F	18	18	1	1

Control group grip strength normality data and histogram

N	**Count**	38
	Missing	0
Mean		1.0137
Std. Error of Mean		.02721
Median		1.0000
Mode		1.05[a]
Std. Deviation		.16773
Variance		.028
Skewness		.325
Std. Error of Skewness		.383
Kurtosis		-.613
Std. Error of Kurtosis		.750
Range		.62
Minimum		.74
Maximum		1.36
Sum		38.52



9.17 APPENDIX 8b

Control group reliability study - grip strength left hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
28.00	28.26	0.81	0.995	0.988 to 0.998

Control group reliability study - grip strength right hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
28.95	29.16	1.15	0.988	0.969 to 0.995

Control group reliability study - grip strength ratio

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
1.06	1.05	0.06	0.792	0.537 to 0.914

9.18APPENDIX 8c

Study group reliability study – grip strength affected hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
8.83	9.30	0.55	0.996	0.984 to 0.999

Study group reliability study – grip strength control hand

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
24.74	25.74	0.91	0.998	0.991 to 0.999

Study group reliability study – grip strength ratio (affected: control)

Mean Score 1st	Mean Score 2nd	Standard Error of Measurement	Intraclass Coefficient	95% CI
0.31	0.32	0.03	0.925	0.728 to 0.981

9.19APPENDIX 9

Study exclusion reasons

PT No	AGE	SEX	REASON FOR EXCLUSION
1	74	F	Takes 5g Vitamin C daily
2	80	F	Lives in Dorset normally and unable to return for follow up
3	84	F	Patient refusal
4	70	F	Presented more than one week post injury
5	83	F	Patient suffers with dementia/memory loss
6	76	F	Fracture requires internal fixation
7	87	F	Patient suffers with dementia/memory loss
8	75	F	Sustained bilateral wrist fractures
9	97	M	Dementia/ipsilateral humeral fracture
10	73	F	Presented more than one week post injury
11	74	F	Recent bereavement and patient refusal (injury at husbands funeral)
12	88	F	Previous cerebrovascular accident and Parkinsons disease
13	71	F	Bilateral Dupytrens disease affecting hands
14	74	F	Patient suffers with dementia
15	61	F	Takes 500mg ascorbic acid daily
16	54	F	Ipsilateral humeral fracture
17	74	F	Patient refusal
18	89	F	Patient suffers with dementia
19	56	F	Fracture requires internal fixation
20	86	F	Patient suffers with dementia
21	82	F	Patient registered blind
22	77	F	Patient suffers with Parkinsons disease
23	86	F	Patient suffers with dementia
24	76	F	Fracture requires internal fixation
25	72	F	Presented more than one week following injury
26	66	F	Fracture requires internal fixation
27	71	M	Non English speaking patient
28	55	F	Open wrist fracture sustained
29	65	F	Skeletal metastases from primary breast carcinoma both humeri

9.20APPENDIX 10

Study withdrawals following trial inclusion and randomisation

PT No	AGE	SEX	REASON FOR WITHDRAWAL
12	54	F	Patient withdrew, not wishing to participate in trial follow up
37	80	F	Patient developed dementia following further fall and subsequent hip fracture
43	60	F	Patient withdrew, not coping with medication and not wishing to participate in trial follow up
56	77	F	Patient developed significant cervical radiculopathy secondary to long standing neck injury following wrist fracture
101	51	M	Unable to contact patients and therefore lost to follow up
113	59	F	Patient withdrew, not wishing to participate in trial follow up
137	62	F	Patient withdrew, not wishing to participate in trial follow up
151	83	F	Patient withdrew, not wishing to participate in trial follow up
158	58	F	Unable to contact patients and therefore lost to follow up
165	54	F	Unable to contact patients and therefore lost to follow up
175	91	F	Patient withdrew, not wishing to participate in trial follow up
187	86	F	Patient withdrew, not wishing to participate in trial follow up
191	62	F	Unable to contact patients and therefore lost to follow up
200	74	F	Unable to contact patients and therefore lost to follow up
212	80	F	Patient withdrew, unable to swallow medications and not wishing to participate in trial follow up

9.21APPENDIX 11

Patients excluded from study per protocol analysis

Pt No	Age	Sex	Reason
9	79	F	Study medications not completed
11	75	M	Study medications not completed
13	80	F	Study medications not completed
14	79	M	Study medications not completed
46	83	F	Study medications not completed
63	50	F	Study medications not completed
66	78	F	Study medications not completed
74	76	F	Study medications not completed
79	71	F	Study medications not completed
84	74	F	Significant medication break taken during trial period due to illness (medications eventually completed)
99	67	M	Study medications not completed
112	73	F	Study medications not completed
146	81	F	Study medications not completed
162	67	F	Study medications not completed
186	64	F	Study medications not completed
193	80	F	Study medications not completed
288	72	F	Study medications not completed
297	72	F	Late displacement of fracture requiring internal fixation

9.22 APPENDIX 12

Effect of ascorbic acid on the features of complex regional pain syndrome

Per protocol analysis

	Ascorbic acid n=89	**Placebo** n=89	Significance
Visual Analogue Scale Mean (95% CI) Range (max score = 100)	n=89 23.8 (18.4-29.9) 0-98	n=89 19.2 (14.4-24.3) 0-88	U=3608.000 Z=-1.096 p=0.274
Short form McGill pain score Mean (95% CI) Range (max score = 39)	n=88 4.4 (3.2-5.7) 0-27	n=89 3.8 (2.6-5.0) 0-27	U=3633.500 Z=-0.894 p=0.372
Vasomotor Instability Score Mean (95% CI) Range (max score = 11)	n=89 2.4 (1.9-3.0) 0-10	n=89 2.2 (1.7-2.9) 0-10	U=3813.500 Z=-0.439 p=0.662
Dolorimetry ratio Mean (95% CI) Range	n=89 0.88 (0.84-0.93) 0.38-1.30	n=89 0.88(0.84-0.91) 0.20-1.35	U=3909.000 Z=-0.150 p=0.882
Abnormal dolorimetry ratio Yes No	n=89 30(33.7%) 59(66.3%)	n=89 26(29.2%) 63(70.8%)	χ^2=0.417 p=0.628
Index finger circumference ratio Mean (95% CI) Range	n=89 1.09 (1.04-1.15) 0.65-1.88	n=88 1.10 (1.06-1.15) 0.71-1.69	U=3694.000 Z=-0.650 p=0.517
Abnormal index finger circumference Yes No	n=89 14(15.7%) 75(84.3%)	n=88 14(15.9%) 74(84.1%)	χ^2=0.001 p=1.000

Finger stiffness (degrees) (Cumulative ROM difference) Mean (95% CI) Range	n=89 -58 (-76 to -41) -372 to 88	n=89 -66 (-84 to -48) -400 to 56	U=3812.000 Z=-0.431 p=0.668
Abnormal finger stiffness Yes No	n=89 32(36.0%) 57(64.0%)	n=89 35(39.3%) 54(60.7%)	χ^2=0.215 p=0.757
Grip strength ratio Mean (95% CI) Range	n=89 0.56 (0.52-0.60) 0.15-1.17	n=89 0.53 (0.49-0.57) 0.13-1.07	t=0.775 p=0.439
Abnormal grip strength ratio Yes No	n=89 69(77.5%) 18(22.5%)	n=89 71(79.8%) 16(20.2%)	χ^2=0.146 p=0.849
Abnormal hair growth reported Yes No	n=88 15(17.0%) 73(83.0%)	n=89 16(18.0%) 73(82.0%)	χ^2=0.027 p=1.000
Abnormal finger nail growth reported Yes No	n=88 23(26.1%) 65(73.9%)	n=89 36(40.4%) 53(59.6%)	χ^2=4.079 p=0.056
Fine motor control dysfunction reported Yes No	n=88 34(38.6%) 54(61.4%)	n=89 38(42.7%) 51(57.3%)	χ^2=0.302 p=0.647
Tremor reported Yes No	n=88 17(19.3%) 71(80.7%)	n=89 10(11.2%) 79(88.8%)	χ^2=2.236 p=0.149

Reported hand and finger symptoms following distal radial fracture

Per protocol analysis

	Ascorbic acid n=89	**Placebo** n=89	**Significance**
Any reported pain			
Yes	47 (52.8%)	41 (46.1%)	χ^2=0.809
No	42 (47.2%)	48 (53.9%)	p=0.454
Spontaneous pain			
Yes	27 (30.3%)	24 (27.0%)	χ^2=0.247
No	62 (69.7%)	65 (73.0%)	p=0.740
Exercise induced pain			
Yes	42 (47.2%)	34 (38.2%)	χ^2=1.470
No	47 (52.8%)	55 (61.8%)	p=0.289
Allodynia			
Yes	19 (21.3%)	17 (19.1%)	χ^2=0.139
No	70 (78.7%)	72 (80.9%)	p=0.852

Reported features of vasomotor instability

Per protocol analysis

	Ascorbic acid n=89	**Placebo** n=89	**Significance**
Significant VMI score (>3)			
Yes	31(34.8%)	34(38.2%)	χ^2=0.218
No	58(65.2%)	55(61.8%)	p=0.756
Swelling			
Yes	34(38.2%)	35(28.1%)	χ^2=0.024
No	55(61.8%)	54(71.9%)	p=1.000
Colour changes			
Yes	28(31.5%)	21(23.6%)	χ^2=1.380
No	61(68.5%)	68(76.4%)	p=0.314
Temperature difference			
Yes	41(46.1%)	36(40.4%)	χ^2=0.572
No	48(53.9%)	53(59.6%)	p=0.545
Excessive sweating			
Yes	9(10.1%)	5(5.6%)	χ^2=1.240
No	80(89.9%)	84(94.4%)	p=0.405

The relationship of patient reported pain (Visual analogue score) and finger tenderness (dolorimetry ratio).

Per protocol analysis

	Pearson's correlation coefficient
Visual analogue score and Dolorimetry ratio	**0.424 (95% CI 0.280-0.560) p=<0.0001**

The relationship of reported pain and abnormal finger tenderness (dolorimetry ratio <0.83)

Per protocol analysis

	Abnormal dolorimetry n=56	**Normal Dolorimetry** n=122	**Significance**
Any pain symptoms			
Yes	39(69.6%)	49(40.2%)	**χ^2=13.343**
No	17(30.4%)	73(59.8%)	**p=<0.0001**
Spontaneous pain			
Yes	23(41.1%)	28(23.0%)	**χ^2=6.165**
No	33(58.9%)	94(77.0%)	**p=0.02**
Pain on exercise only			
Yes	36(64.3%)	40(32.8%)	**χ^2=15.565**
No	20(35.7%)	82(67.2%)	**p=<0.0001**
Allodynia (mechanical or thermal)			
Yes	19(33.9%)	17(13.9%)	**χ^2=9.510**
No	37(66.1%)	105(86.1%)	**p=0.003**

The relationship of patient reported swelling and index finger circumference.

Per protocol analysis

	Abnormal index finger arthrocircometry ratio n=28	**Normal index finger arthrocircometry ratio** n=149	**Significance**
Patient reported swelling			
Yes	19(67.9%)	49(32.9%)	**χ^2=12.184**
No	9(32.1%)	100(67.1%)	**p=0.001**

The relationship of patient reported finger stiffness and measured finger stiffness.

Per protocol analysis

	Abnormal finger stiffness n=66	**Normal finger stiffness** n=111	**Significance**
Patient reported finger stiffness			
Yes	48(72.7%)	35(31.5%)	**χ^2=28.206**
No	18(27.3%)	76(68.5%)	**p=<0.0001**

The relationship of measured index finger circumference and measured finger stiffness

Per protocol analysis

	Abnormal finger stiffness n=66	**Normal finger stiffness** n=111	**Significance**
Abnormal index finger arthrocircometry ratio			
Yes	22(27.3%)	6(5.4%)	**χ^2=24.242**
No	44(72.7%)	105(94.6%)	**p=<0.0001**

The relationship between reported severe weakness and an abnormal grip strength ratio

Per protocol analysis

	Abnormal grip strength ratio n=139	**Normal grip strength ratio** n=34	**Significance**
Patient reported Severe weakness			
Yes	117(84.2%)	14(41.2%)	**χ^2=27.471**
No	22(15.8%)	20(48.8%)	**p=<0.0001**

The relationship between reported and observed trophic changes in the affected hand.

Per protocol analysis

	Abnormal growth observed	**Normal growth observed**	**Significance**
Patient reported abnormal finger nail growth	n=14	n=163	**χ^2=18.770 p=<0.0001 Fisher's test p=<0.0001**
Yes	12(85.7%)	47(28.8%)	
No	2(14.3%)	116(71.2%)	
Patient reported abnormal hair growth	n=30	n=147	**χ^2=60.409 p=<0.0001**
Yes	20(66.7%)	11(7.5%)	
No	10(33.3%)	136(92.5%)	

The relationship between the development of complex regional pain syndrome and patient demographic variables

Per protocol analysis

	CRPS (n=25)	**No CRPS** (n=154)	**Significance**
Gender			
Male Female	2(8.0%) 23(92.0%)	75(49.3%) 77(50.7%)	Fisher's test p=0.743
Age (Years)			
Mean (95% CI) Range	66.2 (62.6-69.7) 51.0-83.0	69.5 (67.8-71.0) 50.0-92.0	t=-1.517 p=0.131
Smoking			
Yes No	5(20.0%) 20(80.0%)	22(14.4%) 131(85.6%)	χ^2=0.528 p=0.546
Working status			
Working Not working	10(40.0%) 15(60.0%)	42(27.5%) 111(72.5%)	χ^2=1.636 p=0.237
Side injured			
Left Right	12(48.0%) 13(52.0%)	94(61.4%) 59(38.6%)	χ^2=1.611 p=0.272
Dominant arm Affected?			
Yes No	13(52.0%) 12(48.0%)	62(40.5%) 91(59.5%)	χ^2=1.161 p=0.383

	CRPS (n=27)	**No CRPS** (n=169)	**Significance**
Multivitamins			
Yes	5(20.0%)	16(10.5%)	Fisher's test
No	20(80.0%)	137(89.5%)	p=0.183

The relationship between the development of complex regional pain syndrome and fracture management variables

Per protocol analysis

	CRPS n=25	**No CRPS** n=153	**Significance**
Fracture manipulated			
Yes	19(76.0%)	75(49.3%)	**χ^2=6.126**
No	6(24.0%)	77(50.7%)	**p=0.017**
Fracture remanipulated			
Yes	3(12.0%)	16(10.4%)	Fisher's test
No	22(88.0%)	137(89.6%)	p=0.734
No. of days immobilized			
Mean (95% CI)	42.4 (40.0-43.0)	39.3 (38.2-40.6)	**U=1255.000**
Range	29-61	24-65	**Z=-2.425** **p=0.015**
Plaster problems reported			
Yes	7(28.0%)	23(15.0%)	χ^2=2.579
No	18(72.0%)	130(85.0%)	p=0.146
Physiotherapy prior to assessment			
Yes	16(64.0%)	46(30.1%)	**χ^2=10.902**
No	9(36.0%)	107(69.9%)	**p=0.001**

Demographic data

Per protocol analysis

	Ascorbic Acid n=89	**Placebo** n=89	**Significance**
Age (years) Mean (95% CI) (Range)	n=89 69.5 (67.4-71.6) 50.0–91.0	n=89 68.6 (66.7–70.6) 51.1–92.0	t=0.600 p=0.549
Sex Male Female	n=89 11 (12.4%) 78 (87.6%)	n=89 10 (11.2%) 79 (88.8%)	χ^2=0.054 p=1.000
Smoker Yes No	n=89 10 (11.2%) 79 (88.8%)	n=89 17 (19.1%) 72 (80.9%)	χ^2=2.139 p=0.209
Employment Retired Employed Housewife	n=89 61 (68.5%) 26 (29.2%) 2 (2.2%)	n=89 61 (68.5%) 26 (29.2%) 2 (2.2%)	χ^2=<0.0001 p=1.000
Fractured wrist Dominant side? Yes No	n=89 35 (39.3%) 54 (60.7%)	n=89 40 (44.9%) 49 (55.1%)	χ^2=0.576 p=0.544

Fracture management data

Per protocol analysis

	Ascorbic Acid n=89	**Placebo** n=89	**Significance**
Fracture manipulated	n=89	n=89	χ^2=2.984
Yes	41 (46.1%)	53 (59.6%)	p=0.098
No	48 (53.9%)	36 (40.4%)	
Type of anaesthesia used	n=41	n=53	
Biers block	23 (56.1%)	15 (28.3%)	
Haematoma block	7 (17.1%)	18 (34.0%)	
Sedation	11 (26.8%)	19 (35.8%)	
General anaesthetic	0 (0%)	1 (1.9%)	
Fracture remanipulated	n=89	n=89	χ^2=0.059
No	79 (88.8%)	80 (89.9%)	p=0.875
Yes	10 (11.2%)	9 (10.1%)	
Time in plaster cast (Days)	n=89	n=89	U=3443.000 Z=-0.401
Mean (95%CI)	39.8 (38.2-41.4)	39.7 (38.3-41.3)	
Range	27-65	24-64	p=0.690
Physiotherapy after cast removal	n=89	n=89	χ^2=0.099
Yes	32 (36%)	30 (33.7%)	p=0.875
No	57 (64%)	59 (66.3%)	

Trial medicine data

Per protocol analysis

	Ascorbic Acid n=89	**Placebo** n=89	**Significance**
Days recruited post injury Mean (95% CI) Range	n=89 2.9 (2.4-3.4) 0-7	n=89 3.6 (3.1-4.1) 0-7	U=3030.000 Z=-2.055 **p=0.04****
Trial medicines completed? Yes No	n=89 89 (100%) 0 (0%)	n=89 89 (100%) 0 (0%)	χ^2=<0.0001 p=1.000
Trial medicine compliance Bottles empty Bottles not returned	n=89 70 (78.7%) 19 (21.3%)	n=89 66 (74.2%) 23 (25.8%)	χ^2=0.499 p=0.597
Clinical assessment (Days post injury) Mean (95% CI) Range	n=89 81.9 (77.0-86.3) 57-192	n=89 81.9 (71.2-87.3) 54-156	U=3801.000 Z=-0.464 p=0.644